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Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication organ of the Turkish Surgical Association, Turkish Hepatopancreatobiliary Surgery Association and Turkish Association of Endocrine Surgery (TAES). The financial expenses of the journal are covered by the Turkish Surgical Association. The journal is published quarterly on March, June, September and December and its publication language is English.

The aim of Turkish Journal of Surgery is to publish high quality research articles, review articles on current topics and rare case reports in the field of general surgery. Additionally, expert opinions, letters to the editor, scientific letters and manuscripts on surgical techniques are accepted for publication and various manuscripts on medicine and surgery history, ethics, surgical education and forensic medicine fields are included in the journal.

The journal is a surgical journal that covers all specialities and its target audience includes academicians, practitioners, specialists and students from all specialities of surgery.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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TURKISH JOURNAL OF SURGERY

Instructions to Authors

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Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Material and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods (with subheadings), Results, Discussion, , Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Material and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Expert Opinions: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future stud-

ies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Surgical Methods: Images of remarkable, striking and rare cases that emphasize the basic mechanisms of diagnosis and treatment of diseases, express discrepancies and extraordinary situations and explain new treatment techniques and options are evaluated for publication. Display items are important in this type of manuscripts and supporting the manuscript with video (in WMV, AVI or MPEG formats) images can facilitate a faster evaluation process and increase the possibility of publication.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget - Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	250 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	250	15	No tables	10 or total of 20 images
Surgical Methods	500	No abstract	5	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIEID/cid.htm.

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When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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Contents

Invited Reviews

Original Investigations

Surgical Technique

TURKISH JOURNAL OF SURGERY

Case Reports

TURKISH JOURNAL OF SURGERY

Editorial

Dear colleagues,

We are happy to be presenting the third issue of this year. Each issue of our journal is getting better with a better quality than the previous one. This issue includes valuable clinical and experimental studies.

We receive many article submissions to our journal both from within our country and abroad. This article flow is important in sustaining the improvement of our journal's quality. That is why, I would like to thank all our colleagues who submit their studies for publication in our journal.

I would like to ask for your further interest to keep this article flow in the future.

The September issue includes a review article, 12 clinical and experimental studies and 9 case reports. The case reports that have been submitted to our journal are being published according to a schedule. We are trying to publish the clinical and experimental studies with priority in order to maintain their actuality. The contribution of our colleagues and its continuance is important.

Our journal can be a part of journals that are being cited by international indexes only if it can be published in a timely manner, if it includes quality studies and if it receives numerous international citations. It is important that studies that will receive citations are submitted to our journal and that articles that have been published in our journal are being used as references in your manuscripts to be published in other journals within those indexes.

I would like to thank in advance for your support and contributions.

Wishing success in your further studies.

Prof. Mustafa Şahin

Editor in Chief

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Invited Review

Advances in small bowel transplantation

Alp Gürkan[1,2]

ABSTRACT

Small bowel transplantation is a life-saving surgery for patients with intestinal failure. The biggest problem in intestinal transplantation is graft rejection. Graft rejection is the main reason for morbidity and mortality. Rejection has a negative effect on the survival of the graft. While 50%-75% of small bowel transplantation patients experience acute rejection, chronic rejection occurs in approximately 15% of patients. Immune monitoring is crucial after small bowel transplantation. Unlike other types of transplantation, there are no non-invasive or reliable markers to predict rejection in small bowel transplantation. The diagnosis of AR is confirmed by clinical symptoms, endoscopic appearance, and pathological specimens taken by endoscopy. Thus, histopathological examinations obtained by protocol biopsies remain as the gold standard for intestinal graft monitoring; however, biopsies have some complications, especially in small grafts. In addition to the high complication rate, biopsies are non-diagnostic; thus, multiple biopsies should be performed to exclude rejection. Therefore, auxiliary assays, such as measurements of citrulline and calprotectin in the blood, cytofluorographic examination of peripheral blood immune cells, cytokine profiling, and distinct gene-set-change measurements, are increasingly being used in small bowel transplantation. Developments in the understanding of genes seem to be promising that limited gene sets, taken from blood or from intestinal biopsies, will enhance pathological diagnosis. Bone marrow mesenchymal stem cell transplantation with SBT and tissue engineering are also promising procedures.

Keywords: Small bowel transplantation, intestinal transplantation, stem cell transplantation, small bowel insufiency, short bowel syndrome

INTRODUCTION

Small bowel transplantation (SBT) has developed slower and has been performed less than other solid organ transplantations. However, it is the most effective and life-saving procedure for patients with intestinal failure who develop complications related to parenteral nutrition. The annual number of SBTs is less than that of all other types of solid organ transplantations. Although the number of SBTs has been decreasing in the United States since 2007, because of bowel rehabilitation programs and recent developments in surgical techniques such as tapering enteroplasties, the number of SBTs has substantially increased in the last 5 years in Europe, China, and Japan (1). It is estimated that 2 or 3 persons per million per year experience intestinal failure, and 15% of them become candidates for SBT (2). The mortality rate is around 40% in 5 years in patients having less than 50 cm of healthy small bowel remaining. Infections and/or thrombosis of vessels and liver disease developing within 2 years after SBT are the most common reasons of mortality.

Small bowel transplantation is a sophisticated procedure for patients with desperate clinical conditions. It covers a number of surgical procedures depending on organs to be transplanted, but the main procedure is the transplantation of the small bowel. Although there are different classifications for the procedure, the most common one classifies it into four groups, according to the inclusion of the liver and/or the stomach in the graft: isolated, liver–intestinal, multivisceral, and modified multivisceral transplantation (3). Although combined liver and SBT used to be the most common procedure in the past, the rate this type of SBT has decreased from 68% to 39% from 2007 to 2011. The number of isolated small bowel transplantations has been increasing due to early referral to the transplantation units (4). SBT patients need more intense immune suppression protocols than other solid organ transplantation patients due to large size of the graft and the strong immune response usually evoked. Thus, opportunistic infections and neoplastic diseases are seen more commonly in SBT than in other solid organ transplantations. Besides, because of the large size of tissue transplanted, graft versus host disease (GVHD) is also more common in SBT than in other solid organ transplantations.

Currently, patients who experience complications in parenteral nutritional therapy are candidates for SBT. Nowadays, SBT is not indicated for patients who are dependent on parenteral nutrition, having

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no complications. Indications for STB are thrombosis of two of the six major venous accesses, episodes of catheter-related infections (two or more per year, fungemia, shock, or respiratory failure), liver disease, alterations of growth and development in children, and refractory electrolyte changes.

CLINICAL AND RESEARCH CONSEQUENCES

Surgical Techniques

Some other abdominal organs can be transplanted with a small intestinal graft, depending on the pathology. Patients with mild liver disease, revealing no signs of portal hypertension and mild hepatic fibrosis on liver biopsy, may receive an isolated intestinal graft and do not need a liver graft transplantation. On occurrence of dysmotility of the foregut with apparent problems, the stomach can be included in the graft. The preferred technique is harvesting and implanting the liver, duodenum, head of pancreas, and small bowel with bile ducts en bloc as a composite graft without damaging the vascular or other structural connections of the organs. The organs can also be harvested from the donor separately and transplanted individually, which is known as non-composite combined liver and SBT. The organs to be transplanted are decided according the underlying disease, presence and severity of liver disease, condition of other organs, and the number of previous abdominal surgeries. An isolated small bowel graft (Figure 1) is indicated in the patients with intestinal failure without a severe hepatic dysfunction. The severity and reversibility of the liver disease is diagnosed by liver biopsy. A recent study claimed that bilirubin levels, platelet count, and albumin levels in children receiving parenteral nutrition show a good correlation with the severity of the hepatic disease (5). Occurrence of bridging fibrosis or cirrhosis indicates that the liver should be added to the intestinal graft. In order to harvest the liver and intestine en bloc, the pancreaticoduodenal arc should be included in the graft. This avoids the dissection of hilar structures, which can be difficult in a donor of pediatric age. Alternatively, liver and intestine can be implanted separately. Thus, in case of severe rejection, the intestinal graft can be explanted easily without removing the hepatic graft. However, separate grafts require multiple vascular anastomosis and biliary reconstruction which cause higher risks of complications.

The superior mesenteric artery is anastomosed to the aorta. Venous anastomosis is performed between the superior mesenteric vein and the inferior vena cava (Figure 2) or the mesenteric portal system. Anastomosis to the portal system is more physiologic and has some possible immunologic advantages, but accessing the recipient's mesenteric portal system is technically more challenging than systemic drainage. In patients with mild portal hypertension with low platelet counts, absence of gastroesophageal varices, and intrahepatic cholestasis with moderate splenic enlargement, venous drainage of the isolated small bowel can be performed into the vena cava. Although the cumulative episodes of infection were higher in patients with drainage into vena cava where the protective effect of the liver is by-passed, a survival difference could not be achieved (6). In practice, anastomosis to the mesenteric superior vein is seldom associated with major problems in terms of outcome; therefore, it is performed more often because of technical simplicity. To observe the bowel endoscopically and obtain biopsies facilitating the diagnosis of rejection and perfusion disorders, ileostomy is performed in all types of SBTs.

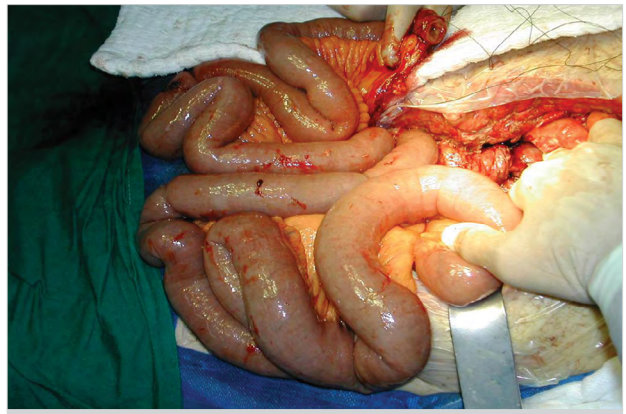

Figure 1. Isolated intestinal graft

Figure 2. Mesenteric venous and arterial anastomosis of the small intestinal graft

Pediatric patients more commonly require combined liver and SBT compared with adults, due to irreversible liver damage, which is more often seen in the pediatric population under parenteral nutrition. However, both grafts are scarcely available for pediatric patients due to size problems. According to the US data, 74% of patients for intestinal transplantation need the combined liver and intestinal graft transplantation (7). Progression of the allocation system and early referral to SBT can help solve this problem.

Inclusion of the colon and spleen to intestinal grafts is controversial. Patients who receive an intestinal graft without the ileocecal valve usually do not have well-formed stools and are more likely to become dehydrated. It was thought that inclusion of the colon in small intestine grafts increases death rates and the risk of graft failure; therefore, this was previously avoided. However, recent studies have shown that inclusion of the colon does not increase morbidity, mortality, and bloodstream infections, and has benefits especially in pediatric patients (8).

Patient's liver, spleen, and pancreaticoduodenal complex should be preserved whenever possible. Different modifications can be applied for patients who need multivisceral transplantations with intact hepatic functions, especially those with Gardner and pseudo-obstruction syndromes. Sparing the native spleen also has potential advantage of reduced risk of post-transplant lymphoproliferative disorders. After showing the beneficial effect of spleen transplantation in promoting

tolerance in animal experiments, a recent research demonstrated that adding the spleen to the multivisceral transplantation graft yielded better outcomes in terms of low acute rejection (AR), without altering the incidence of GVHD (9, 10). Implantation of the donor spleen with liver–intestine graft is advantageous with reduced infection rate and enhanced mixed chimerism. Harvesting the distal esophagus within the multivisceral graft simplifies the transplantation procedure of foregut organs.

Although microendoscopy is not widely used, it helps visualize the transplant serosal surface and monitor mucosal blood flow of the graft during the surgery. This method is also found to be very sensitive during the postoperative and intraoperative period (11). Thus, this method helps assess the viability of the graft. However, the procedure is technically demanding and not easy to perform in a duration of 1 or 2 hours.

Loss of abdominal flexibility in patients with SBT due to massive adhesions related to multiple prior abdominal surgeries, shortage of appropriate recipient size-matched donors especially in pediatric age, scars on the abdominal wall due to fistulas, ostomies, and edema after reperfusion of the graft make the primary abdominal wall closure straitening. A primary tension-free closure of the abdominal wall is achievable in 50%-65% of patients (12). Although sometimes reduced-size grafts can be used to facilitate primary closure, various strategies have been introduced to reconstruct and enhance the abdominal domain. Some strategies that have been employed are usage of tissue expanders, staged abdominal closure with mesh, bioengineered skin equivalents, acellular dermal matrix, vascularized or nonvascularized rectus muscle fascia grafts, skin grafts, and vascularized abdominal wall transplantation from the same donor (12, 13). Abdominal wall transplantation permits primary skin and abdominal wall closure without causing abdominal compartment syndrome. However, it has some disadvantages such as necessity of a complicated vascular anastomosis, longer surgery time, and higher morbidity rate. The use of an avascular rectus allofascia is also reported with good results (14).

Donor Preparation

Donors ideally should be younger than 55 years and under no or low dose of vasoactive drugs (below 5µgr/kg/min of dopamine) abdominal domain of the patients with intestinal failure is usually retracted; therefore, they need smaller donors (30% to 40%). Owing to the development of potent drugs for the prophylaxis and treatment of cytomegalovirus, cytomegalovirus-seropositive donors are accepted, excluding receivers with negative serology. Gastrointestinal tract decontamination and utilization of antibodies for donor lymphocytes have no beneficial effect on prevention of infection, rejection episodes, or incidences of GVHD. These donors are also suitable for harvesting liver and pancreatic grafts. As these grafts share the same bloodstream, it is challenging to simultaneously harvest the grafts, but it is possible to perform the surgery without injuring the grafts.

The mucosa of the small bowel is very sensitive to ischemic injury. Infection-related mortality rate is higher and the absorptive function is lower if the intestinal graft is taken from non-heart beating donors (NHBDs). The viability of the cells may be determined by histological examinations, and thus, grafts taken from NHBDs may be used if the cells are determined to be viable. An experimental study showed that NHBDs are suitable for SBT (15).

Living donor SBT is a relatively recent type of transplantation, which is suitable especially for children with small bowel failure in whom acute decompensated hepatic failure occurs. To decrease the morbidity and mortality while waiting on the list, living donors can be used successfully. Intestinal grafts contain 150 cm of ileum with or without a left lateral liver graft depending on the liver function of the patient. The largest published case series reports that no changes in lifestyle, work habits, or psychologic conditions of the donors were detected after donation (16).

Organ Preservation

The University of Wisconsin (UW) solution is considered the gold standard for the preservation of all organs of the abdomen. However, many studies have shown that other solutions, such as Celsior and HTK, give results similar to those by the UW solution during ischemic periods up to 8 h in SBT. On comparing UW and HTK, results for graft survival, initial function, endoscopic appearance, and rate of transplant pancreatitis were found to be similar. HTK gives the advantage of better flushing of the microvasculature due to its low viscosity (17).

Postoperative Management and Complications

Surgical complications such as wound infection, fistula, bleeding, and dehiscence may cause rejection episodes and opportunistic infections postoperatively. The biggest problem in SBT is graft rejection. Rejection is the main cause of morbidity and mortality. Rejection negatively correlates with the survival of the graft. 50%-75% of recipients experience acute cellular rejection, most commonly in the first 90 days, while chronic rejection (CR) occurs in 15% of patients (18). Severe rejections in SBT have critical consequences compared with other solid organs, with a mortality rate of 50%.

Immunological Complications

Compared with other solid organ transplantations, SBT is harder to achieve because small bowel is where most of the immune cells reside (more than 80%). Previous studies have shown that the small bowel allograft, particularly the ileal part, is the most vulnerable to AR in frequency and severity when compared with other allografts. It represents the "Achilles heel" of multivisceral transplantation. Besides, within 10 weeks of transplantation, enterocytes inhabit the recipients' small bowel, which makes the graft highly chimeric (17). Thus, the presence of patients' lymphocytes within the bowel submucosa may not necessarily reflect rejection, but this bidirectional exchange of immune cells is responsible for GVHD with 7%-13% incidence rate (18, 19). A retrospective study analyzed GVHD in terms of incidence, risk factors, and impact on survival (18). Young age, recipients with multi-organ grafts, and splenectomized cases were found to be risk factors for GVHD. The effect of donor T cells in the pathophysiology of GVHD has been studied (18). The study showed that the degree of chimerism derived from donor T cells correlates with clinical course of GVHD. In 64% of the patients, clinical symptoms of GVHD were presented, and all of them had detectible donor T-cell chimerism. The study showed that all the patients responded

to increase in immunosuppressive therapy, and three of them died due to sepsis and multi-organ failure.

Another immunological complication is inflammatory bowel disease (IBD)-like disease after transplantation. The incidence of IBD in patients with solid organ transplantation is 10 times more than the expected incidence of IBD in the general population (20). Post-transplant IBD is correlated with cytomegalovirus infection, Epstein–Barr virus infection, post-transplant lymphoproliferative disease, and use of tacrolimus (21). Another possible mechanism can be donor lymphocytes having the genetic information for an abnormal inflammatory response. Further, in colonic mucosa, failure of physiological control by donor-derived regulatory T cells causes intestinal inflammation, which may demonstrate itself as an Arthus-like reaction (22). In a previous study, the use of anti-TNFα showed dramatic clinical and histological improvement in two children (23). Anti-TNFα therapy also has some benefits in treating steroid and thymoglobulin-resistant AR episodes.

In the course of AR, gene expression of TNFα is upregulated soon after transplantation and it increases further (24). This process is associated with immunoregulatory activation and induction of apoptosis and T-cell proliferation (25). Many studies have shown that in patients with refractory AR, infliximab can be a good therapeutic option (26). TNFα mRNA expression is slightly elevated 24 h after transplantation due to ischemia reperfusion injury. On occurrence of AR, 168 h after transplantation, the expression levels of TNFα mRNA increase in the intestinal muscular layer (24).

Rejection

The diagnosis of AR is possible by clinical, endoscopic, and pathological evaluation. The gold standard for the diagnosis of AR is pathologic evaluation by biopsy. Endoscopic observation and biopsies are performed through ileostomy. The endoscopic observation should be performed two to three times in a week in the first three months. Then, it is performed once a month according to the course of transplantation (27). Mucosal erythema, edema, shortened and flattened villi, friability, and ulcerations are endoscopic findings associated with AR. Sensitivity and specificity of endoscopy are 52% and 93%, respectively (27). As the lesions may be absent in some of the segments, on suspicion of rejection, several biopsies should be performed.

Local innate immune activation can easily increase the activity of antigen-presenting cells, and this can increase sensitization to donor antigens. To protect grafts against T-cell mediated rejection, lymphocyte-depleting agents are used successfully for induction and long-term tacrolimus with steroids for maintenance treatment. However, as long as AMR it is relatively insensitive to corticosteroids, antibody-mediated rejection (AMR) still is an important problem in SBT (28).

Some authors have successfully performed SBT and multivisceral transplantation across a positive crossmatch (29). Like other solid organ transplantations, donor-specific antibody (DSA) formation in the serum of the patients is associated with AMR. In contrast with preformed DSA, de novo DSA, which is a potent diagnostic marker for AR and CR, is associated with adverse clinical outcomes (29). De novo DSAs seem to appear in approximately one-fourth of the patients after transplantation as a result of alloreactive humoral responses and are associated with increased incidence of CR and graft loss. Specimens of the intestinal mucosa do not contain mesenteric vascular structures, and C4d staining is nonspecific. Therefore, histologic findings of AMR in SBT are not yet well-defined (30). AMR is one of the main problems for transplantation in pre-sensitized recipients. Further, DSAs are the most important cause of long-term CR and late allograft failure (31). DSAs can be detected by single antigen fluorescent bead assays via Luminex. The underlying pathophysiology of CR and late allograft failure is mesenteric arteriopathy, which is highly associated with DSA and complement development.

Immune Monitoring

Immune monitoring is crucial after SBT. Within 5 years after transplantation, approximately 50%-75% patients experience AR, >10% patients experience lymphoproliferative diseases due to over immune suppression, especially in children, and >10% patients experience CR, which results in graft loss (31).

Small bowel transplantation, unlike other types of transplantation, does not have reliable markers to predict rejection. Thus, protocol biopsies and histopathological analysis still remain the gold standard for allograft monitoring for rejection. However, biopsy also has some complications such as perforation and ulceration, especially in the grafts from young donors. Diagnosis cannot be defined in 30% of biopsies. Therefore, multiple biopsies should be performed to exclude rejection (32). It is recommended to perform systemic biomarker evaluation concomitant with histopathological examination. Among auxiliary assays, increase in use of measurements of citrulline level in the blood, cytofluorographic analysis of peripheral immune cell population, cytokine profiles, and the quantitation of distinct gene set changes have been observed (33-35). Developments in the understanding of genes promise to provide; limited gene sets taken from blood or from intestinal biopsies to enhance pathological diagnosis of rejection.

a. Biomarkers

Myeloid dentritic cells (MDC) are potent antigen-presenting cells and serve as markers for the recipients who are prone to AR. Plasmacytoid CD123 (PCD) dendritic cells have tolerogenic effects, and they gradually increase in number during the rejection-free post-transplant period. A single-center study conducted with 23 children declares that the children who experienced AR had significantly higher MDCs/PDCs ratios compared with non-rejecters (36). The carboxyfluorescein succinimidyl ester (CFSE) mixed leucocyte response (MLR) detects cytotoxic-T- cell proliferation as a predictor of AR in solid organ transplantation. The ratio of donor and third-party-induced proliferative CFSE T cells, which is measured by flow cytometry, was assessed as the immune reactivity index for each subset. Immune reactivity index score of more than 1 shows increased risk of rejection and that of less than 1 signifies reduced risk. The sensitivity and specificity of the test for predicting AR in intestinal transplantation is 87.5% and 83.3%, respectively (37).

It has been shown that microRNAs have a critical role in immune regulation. Data suggests that microRNAs have a critical role in the activation of infiltrating cells during AR in SBT (38). These differences in microRNA expression patterns can

be used to identify new biomarkers and therapeutic targets for immunosuppressive drugs. Wide interpatient variability reduces the ability to set cutoff points for rejection across normal population. Nonetheless, these predictive and discriminative biological markers require further large-scale in-depth studies.

Nucleotide Oligomerization Domain (NOD)-2 is a pattern recognizing receptor and plays an important role in limiting innate immune activation. NOD-2 is found on Paneth cells that sense bacterial residues, dendritic cells, and macrophages. Any malfunction in this sensor may result in the initiation of the rejection process via a misexpression with intestinal antibacterial peptides and other alterations in innate immune responses. Therefore, the immune system being provoked, results in structural shifts seen during rejections. For this reason, suppressing the levels of enterobacteria can be a suitable alternative for the elongation of small intestinal allograft survival. Normally, the recognition of intracellular bacteria controls the antimicrobial peptides secreted by Paneth cells. Patients with NOD-2 polymorphisms who undergo SBT are at significantly greater risk of early rejection, decreased survival, and death due to sepsis. SBT patients who have NOD-2 polymorphisms show higher incidence for early rejections and deaths due to sepsis, and their survival rate may be lower (39).

Besides biomarkers that identify ARs, some markers have been investigated to find out the recipients who are prone to AR attacks. Although these markers have more than 90% sensitivity and specificity for predicting AR and appear to give promising results, routine monitoring in a clinical setting has not been established.

b. Imaging tests

Imaging modalities like positron-emission tomography and other radioactive tracers such as ^{111}In-labeled platelets, radiolabeled white cell scintigraphy, and MRI have been investigated for predicting AR. However, none of these techniques are useful owing to the low number of SBTs; as the small number does not make it possible to interpret any possible changes.

An animal experiment showed that real-time determinations of fluid or/and electrolyte movement through the small intestine could be obtained by measuring luminal fluid changes using a new modified perfusion system together with FITC-inulin (40). By this way, it can be possible to reliably follow-up any intestinal dysfunction.

Laser Doppler monitoring is another invasive method that can be monitored continuously. During this procedure, which is quite easy to perform, the monitoring device should be attached to the intestine. An implantable Doppler, which is very swift and performs continuous monitoring, appears to be the ideal method for monitoring grafts. Although the implantable Doppler is swift and gives a sensitive screening, its sensitivity may be a little low. The process of placement of the implantable Doppler in the intestine at the vascular pedicle may cause some risks, wherein venous congestion may be induced on the thin walls of the visceral veins; however, by placing the monitoring device around the vein of the transplant, an early warning of venous congestion may be detected.

c. Stool tests

Recent discoveries about intestinal flora in various diseases may be helpful in studying the alterations in the bowel microflora after transplantation and examining the intestinal allograft damage. Bowel transplant recipients have shown different alterations in their intestinal microflora. In episodes of rejection, the proportions of phylum Firmicutes and the order Lactobacillales have shown a significant decrease, whereas the phylum Proteobacteria, and especially the Enterobacteriaceae, have increased significantly. In such case Firmicutes can be useful to discriminate active rejection from non-rejection (41). The absolute values determined from enterobacteria to total bacteria ratio showed an improvement in detecting differences between healthy transplants and rejections. Thus, a cut-off point of <49.7% of Firmicutes would find out an active rejection with 90% of sensitivity and 90.9% specificity.

Calprotectin, which is an S-100 protein, released from infiltrating lymphocytes can be estimated by stool testing and these early results seem promising for observing the rejection of intestinal graft prior to the onset of histological changes of AR; wherein calprotectin elevations suggest rejection and normal levels are associated with normal histology. Calprotectin shows up in the fecal content by the migration of neutrophils into the intestine and is a sensitive marker of abnormal activity in inflammatory intestinal diseases (42). It is recommended that the recipients with high levels of calprotectin should undergo intestinal biopsy. Another study showed that recipients with rejection show much higher stool calprotectin levels compared with patients with viral enteritis and those with normal biopsies. This study indicated an optical cutoff level to separate rejections from other diagnoses to be 92 mg/kg with sensitivity of 83% and specificity of 77% (43). Another suggested predictor of rejection is IGF-1. During episodes of intestinal dysfunction, calprotectin levels significantly increase and IGF-1 levels decrease (44). Patients with lowered IGF-1 and raised calprotectin should have enteral feeding interrupted and should be put back on TPN until the cause of high calprotectin levels is determined.

Citrulline is a protein released from enterocytes and levels of citrulline show negative correlation with the function of the small bowel graft (33). From its enterocyte-specific origin, it first gained interest in intestinal failure as a marker. Although diminishing plasma levels of citrulline appear to be associated with mucosal damage, it does not reliably predict rejection. In a recent study, citrulline was assessed as a marker in a patient with a wide variety of intestinal pathologies and lack of a predictor for rejection (44).

Loss of plasma proteins into the gastrointestinal lumen may be detected by the fecal content of alpha-1 antitrypsin. Increased losses into feces can be caused by inflammatory diseases resulting in enhanced vascular wall permeability, gut erosions causing loss of interstitial fluid, increased venous pressure, and lymphatic obstruction (44). Increased losses into feces may be due to loss of interstitial fluid and rise in venous pressure caused by gut erosions, lymphatic obstruction, and enhanced vascular wall permeability due to inflammatory diseases.

d. Other predictors

The motility of the transplanted intestine is very important for the sustainability of the transplant. At the first stage, when

there is no extrinsic signaling, the interstitial cells of Cajal help regulate intestinal motility with their pacemaker function. In case of ischemia, reperfusion, and rejection, immunological and local inflammatory changes in the tunica muscularis of transplanted intestines also cause dysmotility. Therefore, dysmotility can be one of the predictors of AR (45).

Bile acid, serum gentamicin, Granzyme B and perforin, proinflammatory mediator leukotriene E4, and vitamins B2, B5, and B6 were tested as markers for rejection after SBT, but none of these were found to be sufficiently reliable (46).

Immunosuppressive Therapy

Several strategies and immunosuppressive regimens were utilized in SBT (27). In most centers, best results were achieved by anti-lymphocyte antibodies and monoclonal or polyclonal induction therapy (7, 27). Mostly thymoglobulin, alemtuzumab, basiliximab, and daclizumab are used for this induction. Tacrolimus administration for the maintenance of immune suppression is continued; in the first month, levels are kept as 12-15 ng/mL and lowered to 8-12 ng/mL after the first stage (10). As in other abdominal organ transplants, corticosteroids are also used, and removed in accordance with the type of grafts and preference of each center.

Although some improvement has been achieved in controlling rejection after SBT with new immune suppressants, ARs and CRs still show a high rate of occurrence. Therefore, some novel attempts, such as bone marrow mesenchymal stem cell (BMMSC) transplantation in addition to SBT, are being examined (47, 48). BMMSCs, which show an immunosuppressive activity in transplantation, are detected for stopping the immunological refractory cells that attack the transplanted organs. They can also urge and carry on the process of epithelialization of the small intestinal epithelium. An animal experiment showed that the immunoregulatory effect of these cells (BMMSC) was affected by the balance of Th1/Th2, Th17/Treg, the related cytoxines, NK-cell activity, and Treg expansion and that these cells prevented AR in SBT (48). Tolerogenic regiments that provoke Tregs and chimerism and block the development of DSA are future treatment goals to be reached. Current studies have shown that intestinal mucosa repair is enhanced by cell proliferation and/or inhibition of epithelial cell apoptosis, which is enhanced by the BMMSC synthesis. In this setting the released cytokines and growth factors are factors as interleukin-11 hepatocyte growth factor, fibroblast growth factor-2 and insulin-like growth factor-I. Some beneficial effects of BMMSC transplantation with SBT have been shown in clinical settings (47).

Tissue Engineering

Current trials have shown that progress in the description and propagation of small bowel stem cells and tissue engineering developments promise that realistic alternatives to deceased donors can be seen in the future. In an animal model, small sections of small bowel, produced by implanting intestine stem cells on collagen structures, demonstrated improved growth after placing the graft in continuity with remnant bowel surgically (49). Progress in experimental trials have shown that efforts in the future would be toward the amelioration of injured bowels or the trials of creating new intestinal tissues from autologous stem cells.

CONCLUSION

As a conclusion of these developments, morbidity and mortality rates of SBT have decreased, lately. As the experience of the centers increase and the mechanisms of immune alloreactivity are elucidated, authors believe that the success in this field will be enhanced. Stem cell transplantation and tissue engineering are seen as promising procedures for the future.

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The effects of bariatric surgical procedures on the improvement of metabolic syndrome in morbidly obese patients: Comparison of laparoscopic sleeve gastrectomy versus laparoscopic Roux-en-Y gastric bypass

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ABSTRACT

Objective: The objective of this study was to evaluate patients who underwent laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy in terms of weight loss, metabolic parameters, and postoperative complications.

Material and Methods: Data on patients who underwent laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy with a diagnosis of morbid obesity between January 2012 and June 2014 were retrospectively evaluated. Patients were compared in terms of age, sex, body mass index, duration of operation, American Society of Anesthesiologists score, perioperative complications, length of hospital stay, and long term follow-up results.

Results: During the study period, 91 patients (45 laparoscopic Roux-en-Y gastric bypass and 46 laparoscopic sleeve gastrectomy) underwent bariatric surgery. There was no difference between the two groups in terms of preoperative patient characteristics. Both groups showed statistically significant weight loss and improvement in co-morbidities when compared with the preoperative period. Weight loss and improvement in metabolic parameters were similar in both groups. The duration of operation and hospital stay was longer in the laparoscopic Roux-en-Y gastric bypass group. Furthermore, the rate of total complications was significantly lower in the laparoscopic sleeve gastrectomy group.

Conclusion: Laparoscopic sleeve gastrectomy is a safe and effective method with a significantly lower complication rate and length of hospital stay than laparoscopic Roux-en-Y gastric bypass, with similar improvement rates in metabolic syndrome.

Keywords: Morbid obesity, weight loss, metabolic syndrome, surgical complication

INTRODUCTION

Obesity is defined as a body weight 20% greater than the expected weight or a body mass index (BMI) greater than 30 kg/m^2, and is a rapidly spreading public health problem throughout the world (1). BMI over 35 kg/m^2 with severe comorbidities or BMI above 40 kg/m^{2}without complaints is classified as morbid obesity. Dietary and lifestyle changes are inadequate treatment methods in morbid obesity in terms of long-term weight loss (2). Thus, surgery is the only effective treatment of morbid obesity (3, 4). Laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) are the most commonly used methods for surgical treatment. LRYGB is a safe technique that has been applied for many years due to its mal-absorptive effect in addition to its volume-limiting effect (5). The most important disadvantage of this surgical technique is postoperative nutritional deficiencies that require long-term follow-up (6). Since LSG is easy to learn, has fewer complication rates, and has fewer nutritional effects, it is being increasingly used in the surgical treatment of obesity (7, 8).

The increase in body mass index is associated with metabolic diseases such as glucose intolerance, diabetes, dyslipidemia, hypertension and coronary artery disease. The association of obesity and metabolic diseases is called metabolic syndrome (9). In this study, we aimed to compare the effects of two different surgical techniques used for obesity treatment on obesity and metabolic syndrome.

MATERIAL AND METHODS

The data on patients with BMI over 40 kg/m^2 or BMI between 35 and 40 kg/m^2 with serious comorbidities according to the International Federation for the Surgery of Obesity (IFSO) criterion who have been treated by LSG and LRYGB at the Selçuk University Research Hospital, Obesity and Metabolic Surgery Clinic between January 2012 and June 2014 were retrospectively reviewed. The study was conducted in accordance with ethical standards set in the Helsinki Declaration with the approval of the local ethics committee. Patient informed consent was not obtained due to the retrospective nature of the study. However, prior to the operation, the patients were informed about the possible complications of the surgical procedures and informed consents were obtained. The surgical technique to be applied was decided according to patient BMI, co-morbid diseases and patient preference. Patient age, gender, BMI, duration of operation, American Society of Anesthesiologists (ASA) score, perioperative complications, length of hospital stay, and long-term follow-up results were obtained from hospital records. Patients

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with ASA score IV or higher, and those with a history of previous anti-reflux or gastric surgery were excluded from the study.

All patients were assessed for cardiac, pulmonary and endocrinology risk of surgery and anesthesia. Abdominal ultrasound and upper gastrointestinal endoscopy was routinely performed. LRYGB was preferred in patients with evidence of esophagitis on endoscopy. All patients underwent a standard diet protocol in the postoperative period, with liquid diet in the first 1 month and soft diet in the second and third months. After the third month, patients were allowed a normal diet. Vitamin supplements were not prescribed routinely for patients with LSG, they were recommended individually according to postoperative follow-up results. Patients receiving LRYGB were routinely discharged with multivitamin supplements.

Patients were regularly monitored by a member of the surgical team and a dietitian. The first postoperative follow-up was performed at the end of the first week. Subsequent follow-ups were set at 1, 2, 3, 6, 12 and 24 months. Patient medication, BMI, excess weight loss, glucose, HbA1c, cholesterol, blood pressure were recorded.

Surgical Technique

All patients received antibiotic prophylaxis (Cephazolin 2 g IV), and thromboemboli prophylaxis with low molecular weight heparin (Enoxaparin 6000 anti-Xa IU 60 mg) and intermittent pneumatic compression stockings and were operated in the semi-lithotomy position.

The standard 4 port technique was used for LSG. The first port was placed in the abdomen supra-umbilically and CO_2 insufflation was established at a pressure of 12 mmHg. A 5 mm port was placed for liver retraction from the subxiphoid area. The working ports were placed under direct vision from the right and left subcostal lines. Gastric vascular structures on the greater curvature were mobilized by using a vascular sealing device (Ligasure; Maryland, Covidien, CO, USA). The stomach was divided starting 2cm from the pylorus until 1 cm to the angle of His vertically over a 36 Fr calibration tube by using 4-to-6 60-mm staplers (Covidien; Endo-GIATM, Tri-StapleTM, USA). In all patients, the stapler line was sutured with a running suture (V-Loc; Covidien, USA) to prevent bleeding and a silicone drain was placed along the suture line.

Laparoscopic Roux-en-Y gastric bypass was performed with the 7 port technique. The stomach was divided by using 2-3 laparoscopic staplers from the lesser curvature to the angle of His after mobilization of the lesser omentum so as to prepare a gastric pouch of 20-30 mL volume. The jejunum was divided as the alimentary limb would be 150 cm from the Treitz ligament and the biliary limb would be 60 cm. The greater omentum was routinely separated from the transverse colon to prevent tension in the gastrojejunostomy anastomosis. All patients underwent gastrojejunostomy with Orvil™ (Covidien; Autosuture, Mansfield, MA, USA) and 25 mm circular staplers, which were introduced into the stomach orally. The jejunojejunostomy anastomosis was performed with a laparoscopic linear stapler. One soft drain was placed in proximity to the gastrojejunostomy line.

Statistical Analysis

Data were collected by using Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and statistical analyzes were performed by using Statistical Package for the Social Sciences 16.0 (SPSS Inc.; Chicago, IL, USA). Student's t test and chi-square test were used to analyze demographic data. Non-parametric tests were used since the majority of the variables in normal distribution controls were identified to be not normally distributed. Independent two group comparisons were made by Mann-Whitney test, and Wilcoxon test was used for dependent group comparison in each group. Categorical variables were expressed as percentage and continuous variables as mean±standard deviation. P value <0.05 was considered as significant.

RESULTS

A total of 91 patients, 24 male and 67 female, who underwent obesity surgery in our clinic and met the inclusion criteria were included in the study. LRYGB was performed on 45 of the 91 patients and LSG was performed on the remaining 46 patients. Preoperative characteristics of the patients are outlined in Table 1. The operative time in the LRYGB group was statistically significantly high. Also, the patients in the LRYGB group had longer hospital stay. Preoperative BMI was significantly higher in the LRGB group than that of the LSG group. When patients were assessed in terms of comorbid diseases; patients in the LRYGB group were found to have more comorbidities, although not statistically significant. Patients were followed-up for at least 24 months in both groups. The 24-month BMIs were similar in both groups. The initial BMI was higher in the LRYGB group; therefore, excess weight loss was found to be lower in the LSG group. However, this difference was not statistically significant. When patients with metabolic syndrome were compared in both groups; the decrease in fasting blood glucose, cholesterol, and HbA1c levels were similar (Table 2). The mean preoperative insulin dose used by insulin-dependent diabetic patients was 52.71±20.1 units/day in the LSG group, and 55.47±23.3 units/day in the LRYGB group (Table 3, 4). At the 12th month postoperative follow-up, daily insulin doses were decreased down to 12.1±9.1 units in the LSG group, and 8.9±7.3 units in the LRYGB group. At the end of the second year, there were no patients in both groups who required insulin treatment. Oral anti-diabetic medication was required in 1 (2.2%) patient in the LRYGB group, and in 2 (4.3%) patients in the LSG group due to partial remission in diabetes mellitus. When the groups were compared in terms of cholesterol levels, the preoperative levels and the decrease rate of cholesterol levels at 24 months were similar. There were no mortalities during the study period. Complications of surgical groups are listed in Table 5. One patient underwent an endoscopic expandable stent replacement due to a stapler line leakage in the LSG group. The stent was removed at 4 weeks after endoscopic and radiological confirmation of leak closure. Another patient in the LSG group developed postoperative bleeding that was controlled by conservative methods. Surgical site infection of the port site where the stomach has been extracted was treated with drainage and oral antibiotics in 3 patients. In the LRYGB group, 2 patients were treated for postoperative bleeding, 4 for surgical site infection, and 3 for anastomotic leak. All bleedings were controlled by blood transfusion and did not require re-operation. Anastomotic leak in the gastrojejunostomy anastomosis was successfully closed with

Table 1. Patient demographics

	LSG (n=46)	LRYGB (n=45)	p
Age (years)*	38.2±13.1	37.8±11.3	NS
Gender#			NS
Female	35	32	
Male	11	13	
BMI (kg/m^2)*	44.1±3.6	48.6±4.8	
ASA score#			NS
I	26 (56.5)	24 (53.4)	
II	16 (34.7)	15 (33.3)	
III	4 (8.6)	6 (13.3)	
Co-morbidities#			NS
Hypertension	13 (28.2)	12 (26.6)	
Type 2 diabetes	14 (30.4)	18 (40.0)	
Glucose intolerance	10 (21.7)	11 (24.4)	
Dyslipidemia	11 (23.9)	12 (26.6)	
Follow-up*	26.2±2.1	28.1±5.6	NS

Results*: expressed as mean±standard deviation; #: n (%)

NS: not significant; BMI: Body Mass Index; LSG: laparoscopic sleeve gastrectomy; LRYGB: laparoscopic Roux-en-Y gastric bypass; ASA: American Society of Anesthesiologists

Table 2. Postoperative 24-month patient data according to surgery type

	LSG (n=46)	LRYGB (n=45)	p
%EWL#	75.3±16.2	79.3±15.4	NS
Blood glucose decrease percent (%)	42.8	44.8	NS
HbA1c decrease percent (%)	33.9	35.0	NS
Cholesterol decrease percent (%)	22.8	25.1	NS
Hypertension medication discontinuation (%)	82.3	88.6	NS

#Expressed as mean±standard deviation

NS: not significant; %EWL: percentage of excess weight loss; LSG: laparoscopic sleeve gastrectomy; LRYGB: laparoscopic Roux-en-Y gastric bypass

Table 3. Follow-up data on patients with LSG

	Preoperative	Postoperative 12 month	Postoperative 24 month
BMI (kg/m^2)	44.1±3.6	33.0±3.1*	29.0±2.9**
Glucose (mg/dL)	180±42.6	114±35.3*	102.5±20.1**
HbA1c (%)	7.9±1.1	5.6±0.9*	4.9±0.8**
Insulin dose (unit)	52±10.1	12±5.6*	0**
Cholesterol (mg/dL)	198.5±44.4	182.0±32.4*	167.0±36.5**

Expressed as mean±standard deviation

*,**(p<0.05): Indicates significant result as compared to preoperative values

LSG: laparoscopic sleeve gastrectomy; BMI: Body Mass Index

Table 4. Follow-up data on patients with LRYGB

LRYGB (n=45)	Preoperative	Postoperative 12 month	Postoperative 24 month
BMI (kg/m^2)	48.6±4.8	34.6±4.6*	30±2.1**
Glucose (mg/dL)	183±39.5	114±33.2*	101.5±20.7**
HbA1c (%)	8.0±1.6	5.4±2.1*	5.2±1.0**
Insulin dose (unit)	56±9.8	8±2.6*	0**
Cholesterol (mg/dL)	199.5±51.3	178±30.8*	156±26.2**

Expressed as mean±standard deviation

*,**(p<0.05): Indicates significant result as compared to preoperative values

LSG: laparoscopic sleeve gastrectomy; BMI: Body Mass Index

Table 5. Operative data and complications

	LSG (n=46)	LRYGB (n=45)	p
Operation duration (minutes)*	66.2±12.1	107.5±32.1	<0.05
Hospital stay (days)*	5.1±2.1	6.2±2.1	<0.05
Complications			<0.05
Bleeding#	1 (2.1)	2 (4.4)	
Stapler line/ anastomosis leak#	1 (2.1)	3 (6.6)	
Surgical site infection#	3 (6.3)	4 (8.8)	
Anastomosis stricture#	-	2 (4.4)	
Conversion to open surgery#	-	1 (2.2)	
Mortality#	-	-	

Results *: expressed as mean±standard deviation; #: n (%)

LSG: laparoscopic sleeve gastrectomy; LRYGB: laparoscopic Roux-en-Y gastric bypass

application of endoscopic fibrin glue to the first two patients. However, revision of jejunojejunostomy anastomosis was required with surgery in one patient. Two patients in the LRYGB group needed balloon dilatation due to anastomotic stricture. There was no conversion to open surgery in the LSG group or the need for an extra port. One patient in the LRYGB group required conversion to open surgery due to bleeding in short gastric vessels.

DISCUSSION

The most important finding in this study is that LSG is as effective as LRYGB in improving weight loss and obesity related comorbidities. However, when the results of the study were evaluated it should be kept in mind that the study was retrospective, the groups were not randomized, and patients with LSG had lower BMIs.

The complication rates are higher in LRYGB and it requires advanced surgical experience. Although surgeons performing the operations in this study are experienced in laparoscopic procedures, the complication rates in the LRYGB group were significantly higher than that in the LSG group. In addition, vitamin and mineral deficiencies are common after LRGB, and most patients require vitamin supplements for a long time (6). LSG is superior to LRYGB in terms of nutritional

deficiencies that may occur in the postoperative period (10). Rapid transfer of stomach contents to the ileum after LRGB is associated with induction of incretins that increase insulin secretion and thus control of blood glucose levels (11). It is known that LSG reduces gastric transit time and as a result it provides early contact of gastric content with the ileum (12). Several studies comparing LSG and LRYGB in terms of type 2 diabetes remission rate showed that the positive effect of LRYGB on glucose metabolism is superior to that of LSG due to its mal-absorptive component (13). However, there is no consensus on this topic in the literature. There are studies advocating that both techniques have no significant superiority over each other in terms of blood glucose and HbA1c levels (14). According to the results of our study, LRYGB was not found to have a statistically significant superiority over LSG in terms of diabetes remission rate. We believe that by providing similar excess weight loss both techniques resulted in elimination of insulin resistance and thus led to comparable results in diabetes remission rate. In addition, elimination of the gastric fundus, which plays an important role in the secretion of ghrelin hormone, in both surgical techniques can provide adequate appetite reduction in patients (15). The gastric fundus is not resected in the LRYGB technique. However, the study by Sundbom et al. (16) showed that vagal denervation of the gastric fundus significantly reduced circulating ghrelin levels. As a result, it is known that any bariatric operation that reduces circulating ghrelin levels provides effective weight loss in the early period (15).

Laparoscopic sleeve gastrectomy has become the most common bariatric surgical method worldwide because of its low complication rate, short learning curve and ease of application (17-19). The most important complications of LSG are hemorrhage and stapler line leakage. Although stapler line leaks are reported at very low rates (0.74-1.7%), they have high clinical significance and may result in prolonged hospitalization, increased morbidity, sepsis, multi-organ failure and death (20-22). In the meta-analysis performed by Rausa et al. (23) the reoperation rate after LRYGB was found to be 1.4-3.1%. In addition, serious complications of LRYGB include bleeding (1.4%), anastomotic stricture (1.4%), infection (1.0%), fistula (0.5%), internal hernia (1.1%), and port site hernia (1.0%) (24).

When the long term results of both techniques are examined, it is reported that LRYGB is superior to LSG in terms of weight loss and resolution of comorbidities. However, LSG can achieve acceptable weight loss with sufficient improvement in comorbidities at 5-year follow-up (25). It is also possible to apply a re-sleeve or gastric bypass technique if patients develop symptoms of weight gain or gastro-esophageal reflux, since they will have a lower body weight than their initial weight.

CONCLUSION

Laparoscopic sleeve gastrectomy, which is prefersred in obesity surgery with its volume-limiting effect, is a safe and effective method that can be applied with less complication rates in comparison to LRYGB along with comparable results in the treatment of obesity related metabolic syndrome.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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Surgeons' approach toward clinical nutrition: A survey-based study

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ABSTRACT

Objective: Although many surgical patients face postoperative problems due to a poor nutritional status, there is evidence that many cases of malnutrition still go unnoticed and untreated in surgical wards. This study aims to define the current attitudes of surgeons toward nutritional screening and support.

Material and Methods: A questionnaire with 13 questions was e-mailed to 1500 surgeons. Cross-queries were made over the responses.

Results: The response rate was 20.9%. Most of the respondents (89.5%) implemented nutritional screening. However, only 24.6% of these surgeons screened every patient for malnutrition. The time to initiate nutritional support varied among respondents, and only 25.5% started nutritional support early enough prior to surgery. Only 9.9% of respondents implemented evidence based practices for preoperative fasting, and 21.2% preferred immunonutrition products for patients undergoing major abdominal surgery for cancer. The responses of surgeons, who participated in at least one scientific meeting on nutrition per year, were more coherent with the nutrition guidelines.

Conclusions: The results of this study reveal that the awareness and knowledge of clinical nutrition need improving amongst surgeons. To increase this awareness and knowledge, continuous learning throughout their career seems essential.

Keywords: Surgeon, malnutrition, nutritional screening, nutrition support, clinical nutrition, awareness

INTRODUCTION

It is a well-known fact that surgical patients with a suboptimal nutritional status have impaired wound healing, impaired immune responses, increased organ dysfunction, delayed recovery, and increased morbidity and mortality (1, 2). However, even though the prevalence of malnutrition is high and may exceed 60% in patients undergoing gastrointestinal or major elective surgeries, many cases of malnutrition probably go unnoticed and untreated in surgical wards (3-6). As the attending specialist, the surgeon must organize nutritional screening and treatment of the patients in a surgical clinic. This necessitates surgeons to have sufficient knowledge of nutrition and to be very sensitive about the nutritional status of their patients. Unfortunately, limited data on the degree of attention paid to this important subject by surgeons suggests that the awareness of nutritional principles may be insufficient among this group of clinicians (5-7). This study displays the results of a survey designed to define the current attitudes of Turkish surgeons toward nutritional screening and support.

MATERIAL AND METHODS

A questionnaire consisting of 13 multiple choice questions was designed by the study authors to investigate the surgeons' approaches to perioperative nutritional screening and therapy of the general surgery patient (Appendix). This survey was e-mailed to 1500 general surgeons, all of whom had already finished the training program in surgery and were working in different hospitals in the Turkish Republic. A cover letter that stood for an informed consent was also attached to this e-mail explaining the purpose of this project and assuring the participants of anonymity.

Since this study was based on a survey answered by doctors, no approval was obtained from any ethics committees; however, the study was conducted according to the Helsinki Declaration.

Only the surgeons who stated that they screened the nutritional status of their patients were asked to answer the questions from 5 to 11 as it was essential to take part in nutritional screening in daily clinical practice to answer these questions.

The answers of each surgeon were stored in a database and cross-queries were made over these responses. The surgeons who were working in state hospitals were compared with the surgeons working in teaching

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hospitals. Further, the answers of respondents were compared according to their experience and the number of scientific meetings on clinical nutrition attended by them in one year.

Statistical Analysis

Chi-Square test (Pearson's Chi-square, continuity correction, and Fisher's exact test) was used to determine association between groups for categorical variables. Descriptive statistics were presented as frequencies and percentages. A p-value less than 0.05 was accepted as statistically significant. Data analysis was performed using Statistical Package for Social Sciences 15.0 (SPSS Inc.; Chicago, IL, USA) software package.

RESULTS

Three hundred and fourteen surgeons (20.9%) responded to the questionnaire. Only the first question was answered by all participants. The ratios are given according to the number of the responders of each question. Fifty-two of the surgeons who responded to this survey (16.6%) had been working for less than 5 years, and 262 (83.4%) had been working for more than 5 years. One hundred and eighty-six surgeons were working in teaching hospitals (62.6%), and 111 (37.4%) were working in state hospitals. This question was not answered by 17 surgeons. The number of surgeons who did not attend any scientific meetings on nutrition in a year was found to be 116 (37.4%), whereas that of those who attended 1-2 and more than 2 meetings in a year was 156 (50.3%) and 38 (12.3%), respectively. The number of surgeons who screened the nutritional status of their patients was 280 (89.5%). Thirty-three surgeons (%10.5) stated that they did not practice nutritional screening in their daily clinical routine.

The surgeons working for less than 5 years had a higher tendency to screen the nutritional status of their patients when compared with the surgeons working for more than 5 years. However, this tendency was statistically insignificant (p=0.140) (Figure 1). The surgeons who participated in at least one scientific meeting on nutrition in a year had a significantly higher tendency to screen the nutritional status of their patients than those who did not participate in any meetings (p<0.001) (Figure 2).

Surgeons working in teaching hospitals had a significantly higher participation in at least one scientific meeting on nutrition in a year when compared with the surgeons working in state hospitals (p<0.001) (Figure 3). Statistical analysis did not reveal a significant relationship between participation in scientific meetings and the duration of surgical experience (p=0.889) (Figure 4).

Significantly more surgeons working in teaching hospitals screened the nutritional status of their patients (p=0.001).

When the respondents who screened for nutritional status were asked which of their patients they screened for malnutrition, 24.6% answered "all of them". The rest of the participants stated that they only screened the patients whom "they thought to be at nutritional risk through inspection" (41.1%) or who were undergoing a major surgery (34.4%). The most frequently used nutritional screening technique was laboratory tests (29.1%), followed by subjective global assessment (24.5%), combined use of different screening systems (23.0%), Nutritional Risk Screening 2002 (19.5%), and anthropometric assessment systems (3.9%). When a patient was determined to be under severe nutritional risk, 20.9% of these participants initiated nutritional support (NS) at 3-4 days prior to surgery, 53.6% initiated it at 5-7 days, and 25.5% initiated it at 10-14 days. The most common method used by the participants to calculate caloric need was to multiply the weight of the patient in kilograms with 25-30 kcal/kg, according to the patients' current clinical status (43.7%). This was followed by the use of the Harris-Benedict Formula (36.1%). One hundred and forty-two surgeons (51.1% of those who screened their patients) stated that in the postoperative period, they always continued NS in the patients whom they gave preoperative NS. One hundred and thirty-five (48.6%) surgeons stated that they continued NS only in the patients who could not fulfill their nutritional needs from oral intake. After discharging from the hospital, 68.8% of the surgeons who practiced nutritional screening recommended the use of oral or enteral NS products to the patients who received support during their hospital stay.

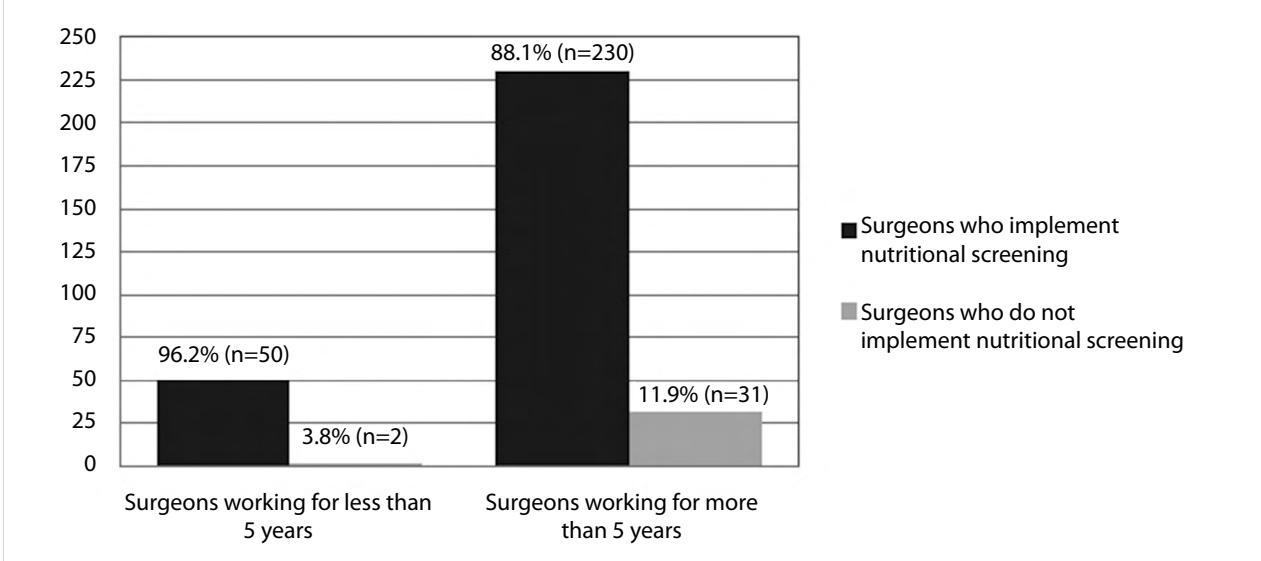

Figure 1. The distribution of the surgeons according to their experience and the implementation of nutritional screening

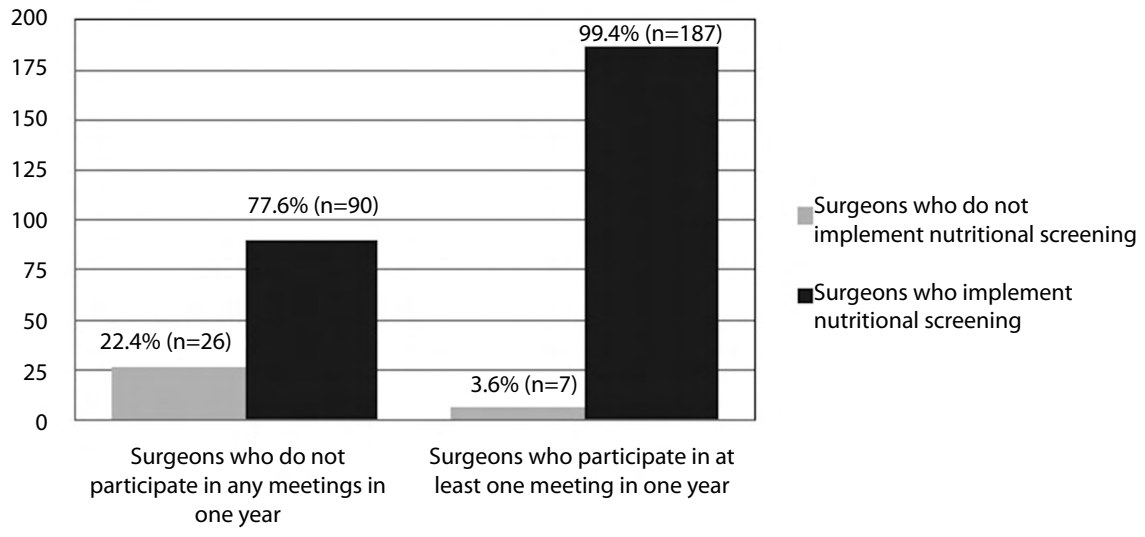

Figure 2. The distribution of the surgeons according to participation in the scientific meetings on clinical nutrition and the implementation of nutritional screening

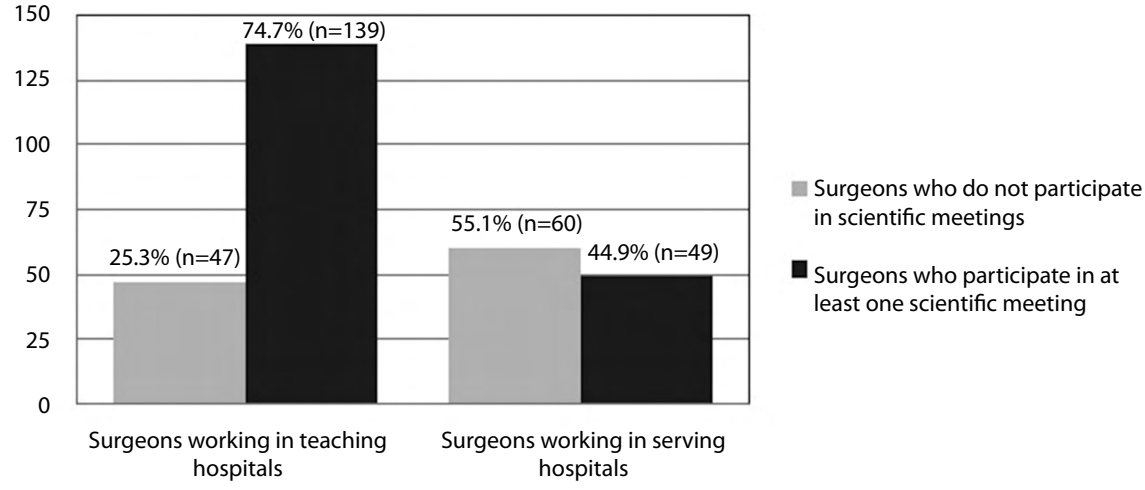

Figure 3. The distribution of the surgeons according to their affiliation and participation in the scientific meetings on clinical nutrition

Forty-seven of 312 respondents (15.1%) ceased oral intake of solid food 6 h before operation. Forty-seven respondents (15.1%), but not necessarily the same respondents who ceased solid food intake 6 h before the operation, ceased the oral intake of clear liquids 2 h before anesthesia induction. Thirty-one participants (9.9%) ceased the oral intake of both clear liquids and solid food preoperatively, according to the American Society of Anesthesiologists (ASA) guidelines for preoperative fasting (8). The participants who attended at least one scientific meeting on nutrition in a year had a significantly higher tendency to act according to these guidelines ($p<0.001$). Further, the participants who attended 3 or more meetings had a significantly higher tendency to act according to the guidelines when compared with surgeons attending 1 or 2 meetings ($p<0.001$).

Sixty-six participants (21.2%) stated that they preferred immunonutrition products for their patients undergoing major abdominal surgery for cancer. Two hundred and forty-four participants stated that they preferred to give standard NS to the patients with severe nutritional risk (78.2%), whereas a small ratio of participants preferred not to give any NS (n=2, 0.6%) to this patient group. A significantly higher number of surgeons participating in scientific meetings on nutrition used immunonutrition in their clinical practice when compared with the surgeons who did not participate in these meetings ($p=0.007$).

DISCUSSION

Depending on the diagnostic criteria, the patient population, and the acknowledged definition, in-hospital prevalence of malnutrition is reported to be between 20% and 50%, and it may even be higher in the surgical wards for certain patient populations (2, 4, 9). Despite these high rates of malnutrition, nutritional practice was shown to be insufficient due to the lack of knowledge and interest among doctors and nurses

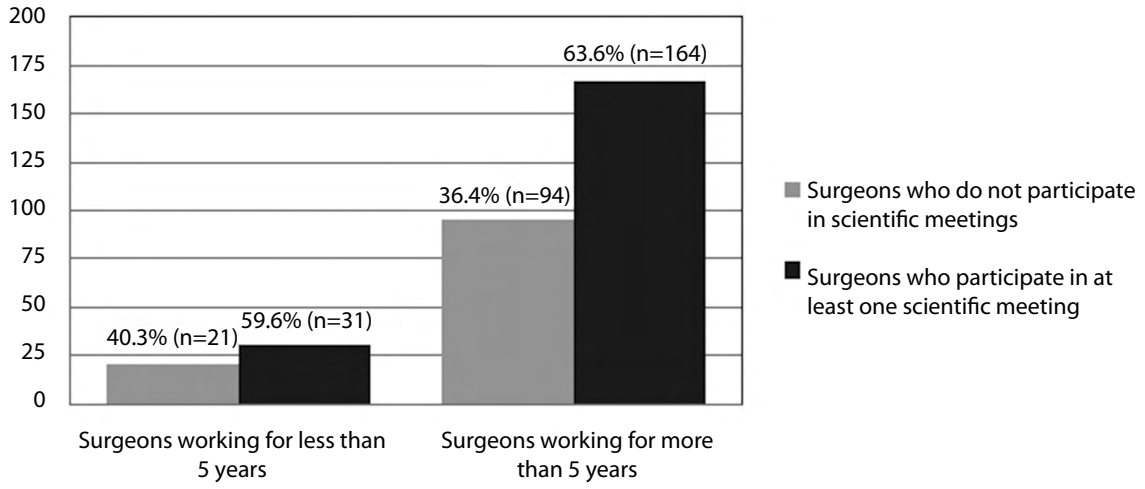

Figure 4. The distribution of the surgeons according to their experience and participation in the scientific meetings on clinical nutrition

(10, 11). Although there are very few studies on the awareness of nutritional topics among surgeons as a specific group of clinicians, present evidence suggests that the knowledge and clinical practices of surgeons may need improvement (5-7). Two of the three studies on the subject demonstrated that the surgical trainees had an insufficient level of knowledge regarding clinical nutrition (6, 7). Another study, which is the only large-scale study on the current practice of general surgeons with regard to clinical nutrition, surveyed the chairmen of the surgery clinics in Switzerland and Austria regarding the current clinical practice at their centers and demonstrated insufficient implementation of nutrition guidelines (5). The aim of the present study was to screen a broad population of general surgeons in Turkey for the awareness of nutritional principles and their clinical practices, as well as to discuss the influence of some potential factors that may affect their tendencies. Our findings demonstrated that most respondents screen the nutritional status of their patients, which suggests a high rate of awareness among these surgeons. The distribution of these participants shows that experience as a surgeon does not affect the surgeons' sensitivity for the nutritional status of their patients. The duration of the experience in surgery also did not seem to affect the surgeons' level of interest toward clinical nutrition in general, as this factor did not influence whether the surgeon attended any scientific meetings on the subject or not. The institutions the surgeons were affiliated with, however, did have a significant influence on the subject of nutritional screening. Surgeons working in teaching hospitals had a significantly higher tendency to screen nutritional status, as well as a significantly higher tendency to attend scientific meetings on clinical nutrition. The findings of the present study also suggest that attending the aforementioned meetings significantly raises the tendency to screen nutritional status.

Only a quarter of the participants, who screened their patients for malnutrition, screened every patient, whereas most of the participants screened only the patients who "looked undernourished" or the ones who would undergo a major surgery. The reluctance to screen every patient at hospital admission is sure to lead to an under-diagnosis of malnutrition, especially in patients who do not appear undernourished. The mentioned reluctance, however, does not seem to be restricted either to our sample group or to general surgeons. Grass et al. (5) have demonstrated in their study that only 20% of the participating surgery clinics in Switzerland and Austria performed routine nutritional screening and only 14% used the nutritional risk score. Further, literature suggests that there is under-recognition of malnutrition worldwide and only a small percentage of malnourished patients receive NS (12-14).

The most commonly used methods for calculating the caloric need were multiplying the weight of the patient by 25-30 kcal/kg and the Harris-Benedict formula. The high percentage of participants using these methods suggests that most of these surgeons are capable of calculating the energy needs of their patients.

However, responses to the question "when to start nutritional support in the preoperative period" were generally not in accordance to the American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines (15, 16). Only a quarter of the participants initiated NS early enough prior to surgery, whereas the timing stated by the rest of the participants to initiate preoperative NS was inappropriate, decreasing the proven potential benefit of preoperative NS. This finding was also in accordance with the only large-scale study on the subject (5). This situation may either be a result of the lack of follow-up of the guidelines or distrust to some of the suggestions in the clinical guidelines by some surgeons. The latter explanation is supported by an Australian survey of surgeons, which revealed a higher confidence in the surgeons' own judgment than in clinical practice guidelines and other sources of evidence (17).

Almost all respondents, who gave preoperative NS, sustained the support in the postoperative period, as also suggested by many authors (18-20). It is also encouraging that almost 70% of participants prescribed oral NS products after hospital discharge to the patients who received perioperative NS. These findings suggest that the postoperative NS these patients receive is acceptable.

Questions 11 and 12 were added to the questionnaire to inquire the opinion of the surgeons on the novel evidence-based approaches for preoperative fasting. Since 1999, American Society of Anesthesiologists recommends the cessation of clear liquids 2 h and solid food 6 h before the induction of anesthesia (8). The continuation of oral feeding in the preoperative period according to these recommendations is also a component of the Enhanced Recovery After Surgery (ERAS) Protocol (21). In this study, only 9.9% of the participants implement the relatively new evidence-based practices in preoperative fasting. However, this tendency of adhering to the traditional approaches does not seem endemic to the Turkish surgeons, as shown by the previously noted low confidence of the general surgeons in clinical practice guidelines (17). There is also evidence that many crucial components of ERAS are not applied in the western world either, and even in centers where ERAS protocol is practiced, there is considerable variation in the compliance to the components of the protocol (22-24). Depending on the data from the present study and the literature, it can be concluded that the widespread implementation of evidence-based perioperative practices including the curtailed preoperative fast needs more time and effort. One way to accomplish this goal may be postgraduate education of surgeons via conferences and scientific meetings. This opinion is supported by the findings of our study, demonstrating that significantly more surgeons attending at least one scientific meeting on nutrition in a year recommend a preoperative fasting protocol according to ASA guidelines. It is also noteworthy that the participants who attend 3 or more meetings in a year have a higher tendency to practice a curtailed preoperative fast when compared with the surgeons who attend 1 or 2 meetings. This finding suggests that these debates and postgraduate education sessions are more effective in changing certain habits when repeated more frequently.

The last question of the survey was about the preference of immunonutrition products. Although there is an ongoing debate on the subject and opposing data in the literature, perioperative use of immune-modulating enteral products in patients undergoing major abdominal cancer surgery independent of the patient's nutritional status is recommended in the current ESPEN guidelines for enteral nutrition (16, 25, 26). These immunonutrition products are reimbursed by the state in Turkey and one would expect the use of such formulas for appropriate indications. However, the results of the present study demonstrate that the use of immunonutrition is not common among participants, so this subject may need more clarification among Turkish surgeons. It is again noteworthy that the surgeons participating in at least one scientific meeting a year have a significantly higher tendency to use immunonutrition in their clinical practice. This may suggest that postgraduate education on clinical nutrition may affect the views of the surgeons.

The findings of the study reveal many issues in clinical practice that need to be addressed. The reason for inadequate awareness of nutritional principles lies in many different grounds. Although lectures on nutrition are given to medical students in many universities in Turkey as a chapter of general surgery, these lectures are usually overlooked by many students for being difficult to understand and for having little influence in the rating of their marks since general surgery has many other chapters. In addition, many university and teaching hospitals lack regular postgraduate education in clinical nutrition for their residents. Thus, a structured education program is imperative in the surgical residency program and this program must include repetitive lectures on clinical nutrition relating to surgical patients. Spear et al. (7) demonstrated in their study that the surgical trainees achieved better results soon after an interactive education program consisting of two 1-h lectures on intensive care unit nutrition. However, when these trainees were tested 3 months after completing the course, the mean test scores were lower than the immediate post-test scores, although still being significantly higher than the pre-course levels. The fall in the degree of knowledge with time necessitates the repetition of the lectures. The results of the present study also support this suggestion, as shown by the higher tendency of the surgeons who attend more than 2 meetings to behave according to the ASA guidelines with regard to preoperative fasting.

The major limitation of the present study is that the questionnaire which was e-mailed to 1500 surgeons working all over Turkey to represent the attitudes of a broad population was answered by a relatively small proportion of these surgeons. This and the lack of acquiring a randomized sample group make it difficult to generalize the data drawn out of this study to all Turkish surgeons. However, the authors believe that the sample size of this study is still rather large enough to give a sound opinion of the present situation. Also, when interpreting the findings of this study, we may speculate that the surgeons who participated in this questionnaire had a higher average degree of interest in topics related to nutrition, resulting in a positive bias. Thus, it is possible to conclude that a much better level of awareness and knowledge in nutrition must be achieved for Turkish surgeons in general.

To increase the awareness and knowledge of clinical nutrition amongst surgeons, continuous learning throughout the career through conferences, congresses, and courses seems essential as suggested by the findings of the present survey. Turkish Society of Parenteral and Enteral Nutrition is very active in taking steps to improve nutritional awareness by holding Life Long Learning® courses of ESPEN in Turkish and independent nutrition courses specifically for topics concerning general surgeons as well as for other disciplines in medicine.

CONCLUSION

The awareness and knowledge of clinical nutrition amongst surgeons needs improving. The findings of the present survey indicate that continuous learning throughout the career through conferences, congresses, and courses is essential to achieve this goal.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Written informed consent was obtained from surgeons who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.O.B., R.H.G.; Design - B.O.B., S.A., T.S., P.E.E.; Supervision - R.H.G.; Resource - R.H.G., B.O.B., P.E.E.; Materials - R.H.G., B.O.B., P.E.E.; Data Collection and/or Processing - B.O.B., S.A., T.S.; Analysis and/or Interpretation - B.O.B., R.H.G., P.E.E.; Literature Search - B.O.B., S.A., T.S.; Writing - Manuscript - B.O.B., S.A., T.S.; Critical Reviews - R.H.G., P.E.E.

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Comparison of contrast-enhanced CT with diffusion -weighted MRI in the Evaluation of patients with acute biliary pancreatitis

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ABSTRACT

Objective: The aim of this study was to compare contrast-enhanced computed tomography with diffusion-weighted magnetic resonance imaging in the evaluation of patients with acute biliary pancreatitis.

Material and Methods: Fifty-three patients diagnosed with acute biliary pancreatitis, between February 2012 and July 2015, were evaluated using diffusion-weighted magnetic resonance imaging and magnetic resonance cholangiopancreatography to explain the elevation of cholestasis enzymes and bilirubin levels at İstanbul University. Contrast-enhanced computed tomography imaging was applied within 8 h following first evaluation. Demographic data, severity of pancreatitis, pancreatic apparent diffusion coefficient, and computed tomography severity index were compared. The significance of the results was evaluated using Statistical Package for the Social Sciences 21.0 program.

Results: Median age was 53.39 (22-90) years in these 53 patients (26 were males and 27 were females). The mean Ranson criterion was 0.96 (0-4) and mean hospitalization duration was 16.02 (3-100) days. Twenty-eight patients were evaluated to have mild acute pancreatitis, whereas 16 were moderately severe and nine were severe based on the Revised Atlanta Classification. Mild pancreatitis score was 0.89, moderately severe pancreatitis score was 3.50, and severe pancreatitis score was 5.78 using the Balthazar score. Elevated C-reactive protein levels were not correlated with necrosis and the clinical severity score ($p>0.05$). There was no significant difference among the Balthazar score, magnetic resonance cholangiopancreatography-apparent diffusion coefficient score, and Revised Atlanta score in the evaluation of the severity of pancreatitis when the two techniques were compared. A statistically insignificant difference was found between the Balthazar score and magnetic resonance imaging results of clinically confirmed necrosis and non-necrosis patients.

Conclusion: It can be concluded that diffusion-weighted magnetic resonance imaging might be better than contrast-enhanced computed tomography in the diagnosis of acute pancreatitis as it avoids radiation exposure as well as the development of renal failure and pancreatitis aggravation due to the use of contrast for computed tomography. These results need to be confirmed with randomized prospective controlled studies.

Keywords: DW MRI, pancreatitis severity, pancreatitis, contrast-enhanced computed tomography

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INTRODUCTION

Acute pancreatitis progresses on an instable course that has exacerbations and remissions. The mortality rate is between 2.1% and 7.8%. Development of necrosis increases mortality in pancreatitis. In patients with necrosis, the mortality rate increases up to 25% (1, 2). Contrast-enhanced computed tomography (CT) is the most important imaging technique to determine the severity of pancreatitis. However, recent studies suggest that the contrast agent for CT aggravates pancreatitis and provokes organ failure. In addition, the inability to administer contrast to patients with renal dysfunction and contrast allergy causes the disease to be assessed insufficiently (3).

Limitations of CT have canalized clinicians to consider different imaging studies. It is believed that diffusion-weighted magnetic resonance imaging (DW MRI) may be compared to and may even replace CT. The severity of acute biliary pancreatitis was evaluated with contrast-enhanced CT and it was compared with DW MRI.

MATERIAL AND METHODS

Patients

The patients diagnosed with acute biliary pancreatitis in the Department of General Surgery of İstanbul University by the School of Medicine using DW MRI and MRCP when cholestasis enzyme levels or bilirubin levels were elevated at the time of initial diagnosis were taken for a CT scan within 8 h. The results of two imaging techniques were compared. None of the patients had imaging contraindications such as metallic implant or claustrophobia for DW MRI. The patients' questionnaire included history of hepatic or biliary operations, hepatotoxic drug use, chronic alcohol use, hepatitis B or C carrier status, and suspicion of periam-

pullary tumor. The patients were excluded from the study in the presence of above conditions. Informed consent was obtained from all participants, and the study followed the guidelines of the Declaration of Helsinki. As this study was retrospectively performed by scanning patient files and imaging methods, it was exempt from institutional ethics committee approval.

The diagnosis of acute biliary pancreatitis was confirmed with increased serum and urine amylase levels. The biochemical parameters such as aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin (TBIL), and direct bilirubin (DBIL) were evaluated at the initial time of admission to the hospital. Ranson value and Balthazar score were also assessed at the initial time of diagnosis and within 24 h. C-reactive protein (CRP) levels at the time of first admission and the highest levels of CRP were recorded.

The cases were classified as having mild, moderate, and severe pancreatitis according to the Revised Atlanta classification. CT scan was performed when the general condition worsened and acute-phase reactants increased. Ultrasound- or CT-guided percutaneous drainage was performed when there was a necessity to drain the collection according to results of imaging techniques. Endoscopic retroperitoneal drainage was also performed when percutaneous drainage was evaluated as insufficient. Cholecystectomy was performed in patients when the pancreatitis regressed prior to discharge.

CT Protocol

Computed tomography was performed in supine position with hands over head, with intravenous contrast using a 16 detector PHILIPS device. The images were taken in the 60th second after the administration of the intravenous contrast. CT severity score was assessed (Table 1) (4).

Diffusion-Weighted Magnetic Resonance Imaging Protocol

Gyroscan Intera Master (1.5 T; Philips Medical Systems, Best, The Netherlands) was used for MRI. DW MRI was performed in the axial plane with a spin-echo echo-planar imaging, single-shot sequence [repetition time (RT) 3505 ms, echo time (ET) 68 ms, fl ip angle, 90°], and b values of 0 and 1000 s/mm^2 with a four-channel sense body coil. A respiratory trigger was not used; the scan was performed under free-breathing conditions. Fifty slices were produced with a 7-mm slice thickness and a 1-mm interslice gap. Other parameters were field of view (FOV), 375 mm; matrix, 124 X100; and double number of samples averaged (NSA) sense factor, 3.0. An apparent diffusion coefficient (ADC) map was obtained for each slice position (5-7).

Statistical Analysis

The results of the evaluation techniques and patient characteristics were compared using statistical methods. The findings were evaluated by IBM Statistical Package for the Social Sciences 21 (IBM Corp.; Armonk, NY, USA). Data was presented as median, minimum, maximum, standard deviation, and mean. The distribution of the variables was analyzed with the Shapiro-Wilk test. In comparison between the two groups, the Mann-Whitney U test was used. Kruskal-Wallis test was used for comparison of more than two groups. Variables of the patients with and without pancreatic necrosis were compared by receiver operator characteristic (ROC) analysis. The results were in the 95% confidence interval and the significance was assessed at the level of $p<0.05$.

Table 1. CT severity score in patients with pancreatitis

Pancreatitis staging in imaging without contrast	Point (A)
Normal pancreas	0
Pancreatic expansion	1
Inflammation of pancreatic or peripancreatic fatty tissue	2
One peripancreatic fluid collection	3
Two or more fluid collections or Retroperitoneal air	4
Pancreatitis staging in contrast enhanced imaging	**Point (B)**
There is not pancreatic necrosis	0
30% > pancreatic necrosis	2
50%>…> %30 pancreatic necrosis	4
50&< pancreatic necrosis	6
CT severity index (CTSI)	A+B
Mild pancreatitis	0-2
Moderate pancreatitis	3-6
Severe pancreatitis	7-10

Table 2. Distribution of patients' biochemical parameters at the time of admission

N=53	Mean	Standard deviation	Median	Minimum	Maximum
WBC	12714	4571	12100	4900	26200
ALT	193	219	70	11	870
ALP	181	162	117	49	709
GGT	274	256	205	10	1092
LDH	613	235	524	256	1135
TBIL	1.9	2.0	1.0	0.30	7.7
DBIL	1.3	1.7	.4	0.01	6.8
CRP	78	126	11	0	436

WBC: white blood cell count; ALT: alanine aminotransferase aspartate; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; TBIL: total bilirubin; DBIL: direct bilirubin; CRP: C-reactive protein

RESULTS

A total of 53 cases (26 males and 27 females) were included in the study; mean age was 55.39 (22-90) years. The median and range values of biochemical parameters, such as AST, ALT, ALP, GGT, LDH, TBIL, and DBIL, of the cases at the time of admission are presented in Table 2.

In our study, mean Ranson values were determined as 1.10 (0-4). The median and range of CRP values of the cases at the time of presentation and when they were the highest were 78.06 (0.2-436) and 243.16 (3.7-640), respectively. Elevated CRP levels and presence of necrosis were not associated with clinical severity. According to the Revised Atlanta Score, 28 cases were mild, 16 cases were moderate, and 9 cases were se-

Table 3. Comparison of clinical severity according to Ranson Score, Apparent diffusion coefficient (ADC), and Balthazar scores

	Mild			Moderate			Severe		
	Mean	Standard deviation	Median	Mean	Standard deviation	Median	Mean	Standard deviation	Median
Ranson	0.68	0.77	0.5	1.31	1.01	1	1.22	0.97	1
Balthazar score	0.89	0.99	0.5	3.5	2.28	3	5.78	2.73	5
ADC	1.33	0.15	1.32	1.38	0.4	1.32	1.57	0.35	1.7

Table 4. Apparent diffusion coefficient (ADC) measurements and necrosis frequency according to pancreatitis severity

		Mild (%)	Moderate (%)	Severe (%)
Necrosis	-	28.0 (100)	13.0 (81)	1.0 (11)
	+	0.0 (0)	3.0 (19)	8.0 (89)
ADC	1.33±0.15	1.38±0.40	1.57±0.35	

ADC: apparent diffusion coefficient

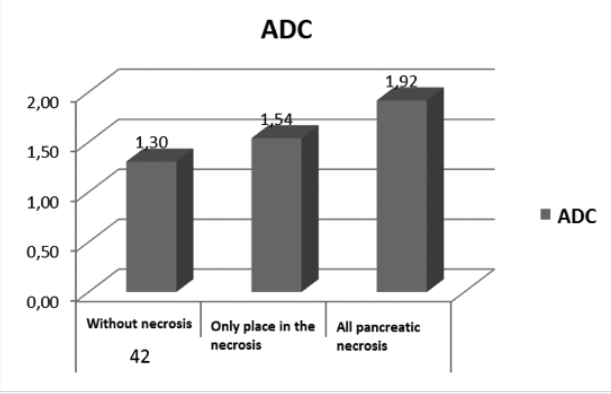

Figure 1. Comprasion based on necrosis location

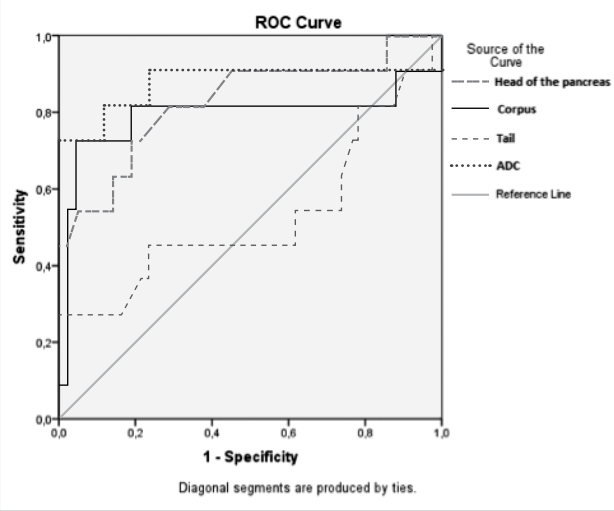

Figure 2. ROC analysis based on necrosis location

vere. Necrosis was observed in all severe cases and in two of the moderate cases. The Balthazar score of the mild, moderate, and severe cases was 0.7, 3.16, 5.37, respectively.

There was no significant difference among the Balthazar score, MR ADC score and Revised Atlanta Score with regard to the evaluation of the severity of pancreatitis when the two techniques were compared. A statistically insignificant difference was found between the Balthazar score and MRI results of clinically confirmed necrosis and non-necrosis patients (Table 3).

Necrosis was not detected in 28 patients who had mild pancreatitis. Necrosis was detected in three of the moderate pancreatitis patients. Necrosis was not detected in one patient who had severe pancreatitis (Table 4).

There was a statistically significant difference in ADC measurements between the patients who had necrosis and those who did not ($p<0.001$). There was also a statistically significant difference between the patients who had a single necrosis zone and those who had multiple necrosis zones (Figure 1, 2).

Four cases were monitored in the intensive care unit. Mean hospital stay was 16.02 days. Laparoscopic cholecystectomy was performed before discharge in 30 cases whose pancreatitis regressed. Percutaneous discharge was performed in two cases. In two of these cases, endoscopic retroperitoneal necrotic debridement was performed because of insufficient drainage. Seventeen cases were discharged after recovery and an elective cholecystectomy was planned. MRI and CT images of two patients are shown in Figure 3, 4.

DISCUSSION

Acute pancreatitis, which is the inflammation of pancreas, can present in a large spectrum, from self-limiting disease to a serious clinical presentation that can lead to sepsis and death. The systemic inflammatory response and complications accompanying pancreatitis cause an increase in disease-related mortality rates (8-10). Despite technological advances, it is debatable to distinguish the patients at increased risk for severe disease at the time of admission to the hospital. For scoring, Ranson criteria, Acute Physiologic and Chronic Health Evaluation (APACHE) II criteria, Balthazar score, and Bedside Index of Severity in Acute Pancreatitis (BISAP) are used (11-14).

In the Revised Atlanta classification, pancreatitis is classified as mild, moderate, and severe. While mortality in mild pancreatitis is <1%, mortality can rise up to 10% in cases with sterile necrosis and up to 30% in cases with severe necrosis (8, 15). The cases in our study were evaluated according to the Ranson criteria, Revised Atlanta classification, ADC values, and Balthazar score. According to Revised Atlanta Scoring, 28 of our cases were evaluated as mild, 16 of our cases were evaluated as moderate, and 9 of our cases were evaluated as severe. There was a difference between the Revised Atlanta Score and Balthazar score in terms of MRADC measurements,

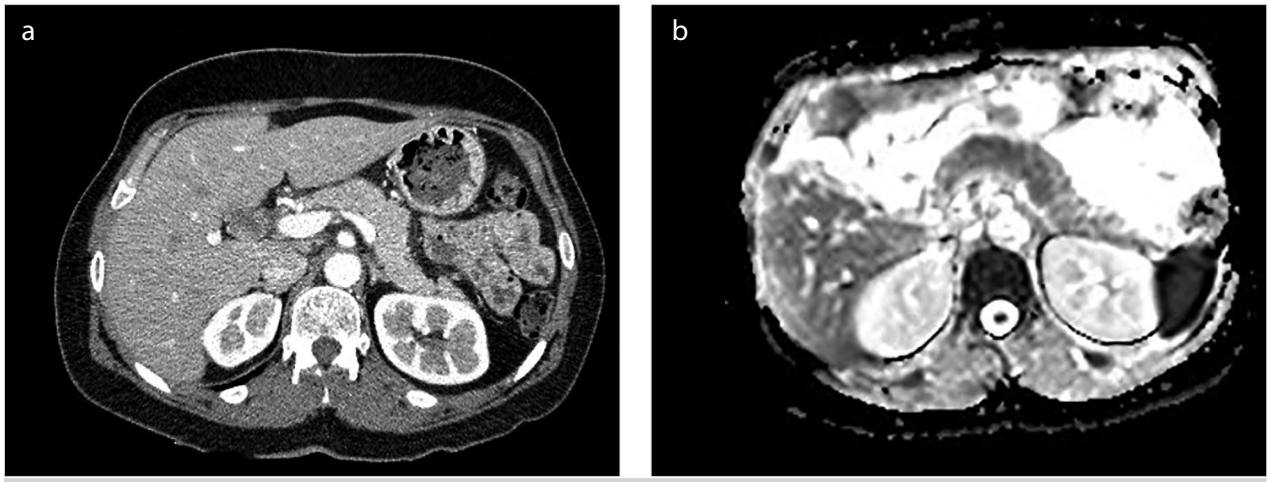

Figure 3. a, b. CT (a) and MRI (b) images of a 40-year-old male patient with necrosis

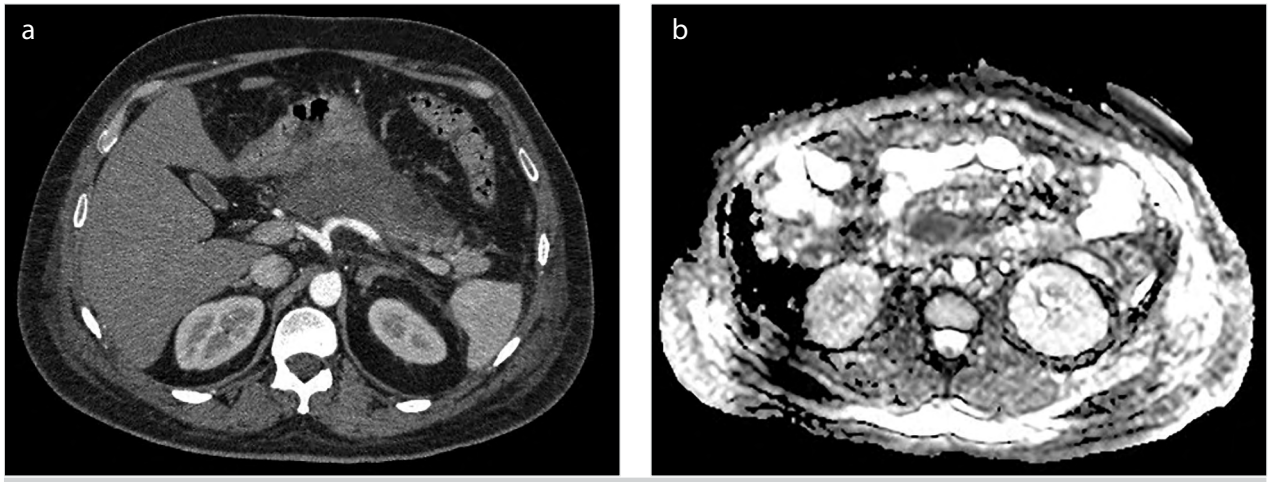

Figure 4. a, b. (a) CT and MRI (b) images of a 48-year-old female patient with acute pancreatitis

which was not statically significant. The mean Ranson value of our cases was determined as 1.10 (0-4).

Intravenous contrast-enhanced CT is an imaging option that can be used for the diagnosis and determination of the severity of the disease. It is important to use CT for early diagnosis and grading of pancreatitis-related complications. CT at the time of first admission is not always necessary, and 15%-30% of CT imagings are non-pathological. The real contraindications for CT are renal insufficiency and contrast allergy. It is emphasized that intravenous contrast can impair pancreatic microcirculation, increase necrosis, and worsen pancreatitis. Despite these factors, CT is necessary to discover other acute abdominal problems that are not caused by pancreatitis.

The mortality rate is 15% in necrotizing pancreatitis. Infected necrosis is seen among one-third of cases with necrotizing pancreatitis. The mortality rate increases in infected necrosis compared with sterile necrosis (16, 17). Infected necrosis can be diagnosed by culture of needle aspiration and presence of air within necrosis can be interpreted as infection.

In order to evaluate acute and chronic inflammation of the pancreas parenchyma, the utilization of DW MRI has recently been established. Decreased ADC values can be due to cellular changes observed in acute pancreatitis. Shinya et al. (18) have reported DW MRI signal intensity changes in acute pancreatitis for the first time. However, their study has not demonstrated a measurable diffusion contrast appearance. In standard T2-weighted imaging, ADC measurement is necessary to differentiate from flare phenomenon (18, 19).

In the study performed by Thomas et al. (19), increased signal activity and decreased ADC measurements have been detected in patients with acute pancreatitis compared with the patients with a normal pancreatic tissue. In this study, ADC values were measured under 1.62×10-3 mm^2 that were evaluated as pancreatitis. When serum leukocyte, amylase, and CRP levels turned back to normal, control imaging was again performed to compare ADC values, which also turned back to normal (19). In our study, ADC measurement was under 1.62×10-3 mm^2 in all patients.

The limitations of our study include its retrospective nature, the paucity of cases, especially those that have necrosis, the fact that DW MRI was not performed when the patient clinically deteriorated, and so that the comparison of necrotic on the CT with DW MRI was also not performed. DW MRI of the patients is obtained either at the time of first admission or within the first week of admission. However, pancreatic necro-

sis generally emerges three to four weeks after inflammation, which demonstrates the necessity for randomized prospective controlled studies.

CONCLUSION

Diffusion-weighted magnetic resonance imaging was superior to CT scan in the evaluation of cases with suspected pancreatitis as there is no radiation and contrast existence that protects the pancreas from exacerbation of pancreatitis. Therefore, DW MRI can be selected in the diagnosis of pancreatitis, especially in patients with organ deficiency, and in differential diagnosis of necrosis, and to decrease the complications of pancreatitis. Prospective randomized studies are needed for defining the definitive role of DW MRI in the evaluation of acute pancreatitis.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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The anti-inflammatory effect of hydrogen sulphide on acute necrotizing pancreatitis in rats

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ABSTRACT

Objective: The aim of this study was to investigate the dose-dependent anti-inflammatory effectof the Hydrogen sulfidedonor sodiumhydrosulphide on acute necrotizing pancreatitis in rats.

Material and Methods: A total of 42 male Sprague-Dawley rats were divided into 4 groups: sham+saline (group 1), sham+NaHS (group 2), acute necrotizing pancreatitis+saline (group 3), and acute necrotizing pancreatitis+NaHS (group 4). Acute pancreatitis was induced in rats in groups 3 and 4 with the infusion of glycodeoxycholic acidinto the biliopancreatic canal and infusion of cerulein parenterally. In group 4, 10 mg/kg NaHS was administered intraperitoneally after cerulein infusion.Tests for liver and kidney function, interleukin-6, lactate dehydrogenase in bronchoalveolar lavage, and malonyaldehyde and myeloperoxidase activities in pancreas and lung tissue were performed, and histopathologic examination of pancreas was conducted.

Results: In groups 3, a significant increase in amylase, alanine aminotransferase, urea, interleukine-6, lungmalondialdehydeand myeloperoxidase activities, pancreas myeloperoxidase activity, edema, and necrosis in pancreas tissue and a significant decrease in serum calcium levels were detected ($p<0.05$). In group 4, addition of NaHS resulted in a significant decrease in lactate dehydrogenase level in bronchoalveolar lavage, amount of urea, lung myeloperoxidase activity, and pancreatic edema ($p<0.05$).

Conclusion: Although not in pancreatic necrosis, hydrogen sulphide has an anti-inflammatory effect especially in the inflammatory process in lung and edema in pancreasin acute necrotizing pancreatitis at particular doses. With further studies evaluating the anti-inflammatory effects of hydrogen sulphide, we believe it can be used in the treatment of edematous acute pancreatitis and the related complications in lungs.

Keywords: Hydrogen sulphide, pancreatitis, rats

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INTRODUCTION

Acute pancreatitis is an inflammatory disorder of the pancreas presenting with abdominal pain and elevated pancreatic enzymes in the blood (1).Gall bladder stones and chronic alcohol usage are the etiologic factors in 80% to 90% of the cases (2). The incidence of pancreatitis ranges from 4.9 to 35 per 100.000. Mortality rates were previously reported 10% to 30%.In necrotizing pancreatitis, mortality rates are reported to increase up to 12% in the case of sterile necrosis, to 30% in infected necrosis, and to 47% in multi-organ failurein previous studies (3, 4).

The pathophysiology of acute pancreatitis is not obvious, although intracellular activation of the digestive enzymes in acinar cells is accepted as the starting point. Free oxygen radicals released from the injured cells and mediators and cytokines from the leukocytes play a major role in the progression of acute pancreatitis and multi-organ failure (5). Autodigestion of pancreas and failure of microcirculation in pancreas are the main mechanisms in the pathophysiology of pancreatitis (6). Acute necrotizing pancreatitis (ANP) is the most severe form of inflammation in pancreas. Coagulation necrosis of the glandular cells and fat tissue are the pathological findings in ANP.

Hydrogen sulphide (H_2S) is a gaseous mediator, which can be endogenously synthesized by cystathionine-δ-lyase (CSE) and cystathionine-β-synthase (CBS) enzymes from L-cysteine aminoacids (7, 8). The synthesis of H_2S is increased in disorders coursing with inflammation like acute pancreatitis, sepsis, and endotoxemia (9). The effects of H_2S on inflammation are conflicting. Inhibition of endogenously synthesized H_2S has previously shown to decrease the inflammatory response (10, 11). With these properties, H_2S was thought to be a pro-inflammatory molecule. The anti-inflammatory property of H_2S was detected in a study conducted with an H_2S-releasing non-steroidal anti-inflammatory drug (NSAID) (diclofenac) whenH_2S provided a more anti-inflammatory response compared with an H_2S non-releasing NSAID (12).

Sidhapuriwala et al. (13) showed the anti-inflammatory effect of H_2S in edematous pancreatitisin their study using H_2S-releasing S-diclofenac. The anti-inflammatory effect of H_2S was also shown

by the inhibition of TNF-α vs. IL-6 in the study of Xu et al. (14) with hemorrhagic shock-induced rats. H_2S inhibits the nuclear factor κβ (NF-κβ), one of the main regulators of inflammation, and decreases proinflammatory cytokines, chemokines, and adhesion molecules (15-17). Further, its antioxidant and anti-apoptotic efficiency have been previously reported (18-20). To the best of our knowledge, no study has evaluated the anti-inflammatory effect of H_2S in necrotizing pancreatitis.

The aim of this study was to investigate the dose-dependent anti-inflammatory effects of H_2S on the histopathology of pancreas and its functions by biochemical parameters in necrotizing pancreatitis in rats.

MATERIAL AND METHODS

This experimental study was conducted with the approval of Ethical Committee of the Surgical Research Laboratory of our hospital.

Forty-two male Sprague-Dawley rats weighing 300-350 g were used in the study. Rats were maintained in routine laboratory conditions, 21°C, 60% to 70% humidity, and 12/12 h light/dark cycle, at our institution'sAnimal Research Laboratory. Rats were divided into four groups. Oral intake was restrictedto water 12 h before the operation. Anesthesia was administered with intraperitoneal 50mg/kg ketamine (Ketalar, Eczacıbaşı) injection. Subsequently, the right internal jugular veins of the rats were catheterized for fluid replacement, and left carotid artery was catheterized for blood sampling.

Group 1 (Sham+saline, n=7): Right jugular vein and carotid artery catheterizationwas performed. Physiologic saline was infused at 8 mL/kg per hour for 24h via the right jugular venous catheter.

Group 2 (Sham+H_2S, n=7): Procedures performed for group 1 were performed and then 10 mg/kg sodium hydrosulphide (NAHS) (Sigma-Aldrich) (Lot No: 06396APV) dissolved in distilled water was administrated intraperitoneally.

Group 3 (ANP+saline, n=15): After jugular vein catheterization, the distal end of thecatheter was placed in the suprascapular region in 15 rats in this group. Subsequently, laparotomy was performed. Bilio-pancreatic duct was catheterized by a transduodenal approach from the antimesenteric sideof the duodenum. Pancreatic fluid was drained with the help of gravity for 5 min. Main hepatic duct was clamped. Then 10-mMol glycodeoxycholic acid (GDOC, Sigma St Louis, 3528) 1.2 mL/kg under 30mmHgpressure was infused via the catheter. This pressure was achieved using a volume-controlled infusion pump (IVAC 7000; United Kingdom Hampshire, Alaris Medical Systems, RG22, 4BS). After infusion, the catheter was removed and the duodenal hole was repaired. Subsequently, cerulein (Sigma & Aldrich Chemie, GmbH, C-9026) was infused for 6 h, 5 µg/kg per hour, with the infusion pump. Following this, serum physiologic was infused at a rate of 8 mL/kg/h for 18 h.

Group 4 (ANPH_2S, n=13): Like group 3, after acute pancreatitis was formed, 8 mL/kg/h serum physiologic and 5µg/kg cerulein was infused; 8 mL/kg Ringer's lactate was infused for the remaining 18 h. After cerulein infusion, 10 mg/kg NaHS was applied to the rats intraperitoneally.

After 24 h, blood samples were collected from the rats for analyzing biochemical parameters and serum IL-6 levels. Blood samples were centrifuged in Eppendorf Centrifuge 5810 machine at 3200 rpm for 10 min for analyzing biochemical parameters. Enzymatic colorimetric analysis of serum samples was conducted for measuring amylase, glucose, urea, creatinine, ALT, and calcium levels using COBAS 6000 machine. Enzyme linked-immunosorbent assay (ELISA) Kit, RayBio®Rat IL-6 (Lot No: 1137545A), was used for measuring IL-6 levels in serum samples. Then thorax was opened by sternotomy. The left lung was clamped from the left main bronchus and a cannula was placed in the trachea. Bronchoalveolar lavage was performed with 2 cc phosphate buffered saline (PBS) solution. Lavage fluid was stored at −20°C in tubes containing EDTA for protein measurement. At the end of the experiment, BAL protein levels were measured by Lowry method (21). COBAS 6000 machine was used for BAL LDH measurement. After this step, pneumonectomy was performed for the left lung, and the extracted tissue freezed in liquid nitrogen for malondialdehyde (MDA) and myeloperoxidase (MPO) measurements.

After all these procedures, laparotomy was performed and the pancreaswas extracted. Previously defined steps performed for the lung were repeated the measurement of MPO and MDA in the pancreas. Part of the pancreas was stored in 10% formaldehyde-containing tubes for histological examination. Tissue analysis in the pancreas and lungwere performed with the method described by Uchiyama and Mihara, by measuring MDA concentration with thyobarbituric acid colorimetric reaction (22). MPO activity was analyzed as described by Bradley et al. (23).

Pathological studies were conducted on slides prepared from pancreas of the rats. Tissue samples were fixed in 10% formaldehyde. The slides were studied under a light microscope to observe necrosis, edema, and granulocyte infiltration. All these pathological changes were histologically evaluated by the same pathologist (Table 1) (24).

Statistical Analyses

For data analyses Statistical Package for the Social Sciences 13.0 (SPSS Inc.; Chicago, IL, USA) was used. Descriptive statistics were summarized with mean and standarderror. Numeric data appropriate for normal distribution were evaluated with Student t test, and those not appropriate for normal distribution were evaluated with Mann-Whitney U test. Appropriateness of normal distribution was evaluated with Kolmogorov-Smirnov test. $P<0.05$ was accepted as statistically significant.

RESULTS

Sham+saline and sham+H_2S groups had no mortality. Four rats in Sham+ANP group and two rats in ANP+H_2S group died (mortality rates 26.6% and 15.2%, respectively). There was a statistically significant difference in 24-h serum glucose, urea, amylase, creatinine, ALT, calcium, and IL-6 levels and hourly urine flow levels between the groups with ANP and those without. H_2S application significantly improved urea and BAL LDH values. Statistical comparison of the groups and significance values are given in Table 2.

Table 1. Histopathological scoring criteria for necrotizing pancreatitis

Score	Description
Edema	
0	Absent
0.5	Focal expansion of interlobar septae
1	Diffuse expansion of interlobar septae
1.5	Same as 1 + focal expansion of interlobal septae
2	Same as 1 + diffuse expansion of interlobar septae
2.5	Same as 2 + focal expansion of interacinar septae
3	Same as 2 + diffuse expansion of interacinar septae
3.5	Same as 3 + focal expansion + intercellular spaces
4	Same as 3 + diffuse expansion + intercellular spaces
Acinar necrosis	
0	Absent
0.5	Focal occurrence of 1Y4 necrotic cells/high power field
1	Diffuse occurrence of 1Y4 necrotic cells/high power field
1.5	Same as 1 + focal occurrence of 5Y10 necrotic cells/high power field
2	Diffuse occurrence of 11Y16 necrotic cells/high power field
2.5	Same as 2 + focal occurrence of 11Y16 necrotic cells/high power- field
3	Diffuse occurrence of 11Y16 necrotic cells/high power field
3.5	Same as 3 + focal occurrence of >16 cells/high power-field
4>	Necrotic cells/high power field (Extensive confluent necrosis)
Inflammation and perivascular infiltrate	
0, 0-1	Intralobular or perivascular leukocytes/high power field
0.5, 2Y5	Intralobular or perivascular leukocytes/high power field
1, 6Y10	Intralobular or perivascular leukocytes/high power field
1.5, 11Y15	Intralobular or perivascular leukocytes/high power field
2, 16Y20	Intralobular or perivascular leukocytes/high power field
2.5, 21Y25	Intralobular or perivascular leukocytes/high power field
3, 26Y30	Intralobular or perivascular leukocytes/high power field
3.5, >30	Leukocytes/high power field or focal microabscesses
4, >35	Leukocytes/high power field or confluent

Malondialdehyde and MPA were measured in pancreas and lung to detect the oxidative injury and to detect the neutrophil infiltration, respectively. MDA and MPO in lung and MPO in pancreas were significantly increased in the groups with pancreatitis, and H_2S application was found to decrease lung MPO. Statistical comparison of the groups and significance values are given in Table 3.

On histological examination, edema, necrosis, and cellular infiltration were significantly increased in the groups with pancreatitis. The effect of H_2S application on the decrease of edema was statistically significant. Statistical comparison of the groups and significance values are given in Table 4.

DISCUSSION

In the present study, NaHS decreases mortality, does not have any effect on pancreatic necrosis, improves the organ functions, and has partial anti-inflammatory effects with regard to pancreatitis in ANP.

Different experimental acute pancreatitis models have been defined previously. In the present study, the method of Schmidt et al. (24) for ANP was used. In this pancreatitis modelconstructed using cerulein and glycodeoxycholic acid,elevated pancreatic enzymes, edema of pancreatic tissue, and acinar cell necrosis were observed. This method is the most widely used, safest, and standardized method. Patients usually present to the outpatient clinic 24 to 36 h after the onset of pancreatitis. Therefore, H_2S was given 6 h after the induction of the experiment.

H_2S is a gaseous mediator, which can be endogenously synthesized. H_2S opens the adenosine triphosphate (ATP)-dependent potassium (K^+) channels and relaxes the blood vessels and smooth muscles in the gastrointestinal system. H_2S has a vasodilatory effect (25, 26).

Inhibitionof endogenous H_2S using CSE inhibitors decreases the inflammatory response, showing the proinflammatory effect of H_2S (18, 27). However, in this study, the anti-inflammatory effect of H_2S was observed by comparing the effects of H_2S-releasing NSAID (diclophenac) and H_2S-non-releasing NSAID (14). H_2S-releasing drugs were shown to have anti-inflammatory effects (28). In the study of Sidhapuriwala et al. (29) investigating the anti-inflammatory effect of H_2S using NaHS, an H_2S donor, at 10 mg/kg, a decrease in the inflammation in pancreas and lungs secondary to edematous pancreatitis was observed. The aim of the present study was to evaluate the efficiency of the same dose in necrotizing pancreatitis in rats.

Pancreatic necrosis is the key point in severe pancreatitis and directly correlates with mortality (30). Histological examination is important in detecting the severity of acutepancreatitis. In the present study, edema, acinar necrosis, hemorrhage, fat necrosis, and inflammation in pancreas was evaluated according to the histopathological scoring scale defined by Lowry et al. (21). We found that edema, perivascular infiltration, and necrosis in the pancreatitis group were significantly higher than those in the non-pancreatitis group ($p<0.05$). In the group with NaHS (group 4), edema significantly decreased ($p<0.05$). H_2S had no effects on pancreatic necrosis. The other factor increasing necrosis is apoptosis (31). In the present study, we did not work on apoptosis. Xu DQ et al. (14) showed the anti-apoptotic property of H_2S in their study.

In the present study, the enzyme activity of the lipid peroxidation product MDA was measured to detect the oxidative stress in pancreas and lung tissue due to pancreatitis and that of MPO was measured to detect neutrophil infiltration. Pancreatitis groups showed MDA and MPO increase in pancreatic tissue. Increase in MPO levels was statistically significant ($p<0.05$). MDA and MPO decreased in the group containing

Table 2. Glucose, amylase, ALT, urea, creatinine, calcium levels in serum and LDH and urine levels in BAL in the 24th hour

	Sham+saline (n=7)	Sham+H_2S (n=7)	ANP+saline (n=11)	ANP+H_2S (n=11)
Amilase (U/L)	2328±49	2051±115	10741±2162*	7849±1334
Glucose (mg %)	239±21	149±10	101±9*	122±10
Urea (mg %)	16±1	13±1.2	39±5*	19±5#
Creatinine (mg %)	0.38±0.1	0.44±0.4	0.34 ±0.5	0.28±0.5
ALT (U/dL)	63±3	66±10	247±60*	205±55
Calcium (mg %)	10±0.3	9.1±0.6	8.2±0.2*	8.5±0.12
BAL LDH (U/dL)	368±58	188±25	590±78	229±34#
IL-6	41.2±1.4	157±56	995±419*	1248±467
Urine (mL/hour)	1.05±0.5	0.7±0.2	0.28±0.5*	0.4±0.3

Data are shown as mean±standard error of mean. *p<0.05: comparision of ANP and non-ANP groups; #p<0.05: comparision of ANP+saline and ANP+H2S; ALT: alanine amino transpherase; BAL: bronchoalveolar lavage; LDH: lactate dehydrogenase; IL-6: interleukine-6; SEM: standart error

Table 3. MPO and MDA measurements in lung and pancreas tissue

	Sham+saline (n=7)	Sham+H_2S (n=7)	ANP+saline (n=11)	ANP+H_2S (n=11)
Lung MPO (U/mg protein)	3.8±0.11	3.7±0.76	5.94±0.61*	4.3±0.27#
Lung MDA (nmoL/mgProtein)	1.00±.004	0.74±0.03	1.47±0.14*	1.1±0.08
Pancreas MPO (U/mg Protein)	1.02±0.14	0.82±0.15	1.89±0.37*	1.53±0.26
Pancreas MDA (nmoL/mg protein)	0.38±0.07	1.6±0.44	0.7±0.14	0.69±0.15

Data are shown as mean±standard error of mean. *p<0.05: comparision of ANP and non-ANP groups; #p<0.05: comparision of ANP+saline and ANP+H_2S; MPO: myeloperoxidase; MDA: malonylaldehyde

Table 4. Evaluation of histological edema, inflammation, and necrosis in pancreas tissue

	Sham+saline (n=7)	Sham+H_2S (n=7)	ANP+saline (n=11)	ANP+H_2S (n=11)
Edema	0.4±0.17	0.42±0.1	1.4±0.17*	0.8±0.15#
Necrosis	0.0±0.0	0.7±0.7	1.5±0.21*	1.7 ±0.45
Inflammation	0.7±0.07	0.7±0.7	1.1±0.1*	1.5±0.26

Data are shown as mean±standard error of mean. *p<0.05: comparision of ANP and non-ANP groups, #p<0.05: comparision of ANP+saline and ANP+H_2S

NaHS, but this was not statistically significant. Sidhapuriwala et al. (29) showed in their study with mice that H_2S decreases pancreatic MPO activity.

Platelet activating factor, TNF-α, IL-1, IL-6, and IL-8 are the major cytokines that have a role in pancreatic injury and are the starters of systemic anti-inflammatory response syndrome. In the present study, we used IL-6 to detect the cytokinerole in inflammatory response. The groups with pancreatitis showed statistically significant increase in IL-6 levels (p<0.05). NaHS addition did not show any decrease in IL-6 levels. However, Xu et al. (14) showed that H_2S inhibits TNF-α and IL-6 in their study.

Serum amylase increases in acute pancreatitis. Serum amylase levels are not relevant for severity of pancreatitis, and it is only used in diagnosis (32). In the present study, serum amylase levels in ANP-induced rats at 24 h were increased significantly (p<0.05). Although not reaching a statistical significance, addition of NaHS decreased the amylase levels. Sidhapuriwala et al. (29) showed that 10 mL/kg dose of NaHS decreased serum amylase levels in their studyon edematous pancreatitis. In the present study, serum glucose levels were significantly increased in the pancreatitis groups (p<0.05), but the effect of NaHS on glucose levels was not significant.

Parameters showing multi-organ injury such as serum urea and ALT levels significantly increased in the pancreatitis groups, whereas serum Ca^{++} and urine flow significantly decreased (p<0.05). These parameters were improved in NaHS-administered group. The improvement in urea was statistically significant (p<0.05).

The most common and severe complications of acute pancreatitis are in the respiratory system. Hypoxemia secondary to ventilation/perfusion failure, atelectasis, pleural effusion, lung edema, and acute respiratory distress syndrome (ARDS) are some of the complications (33, 34). The most dangerous complication is ARDS with morality rates of approximately 50%. Coagulopathies in microcirculation, lipase and phospholipase activities; and arteriovenous shunts opened by the release of kinines are the triggering factors leading to the development of ARDS (33). In the present study, LDH in BAL fluid and MDH

and MPO in lung tissue were analyzed to evaluate lung complications. BAL LDH was used to detect lung and lung endothelial injury (35, 36). BAL LDH levels were elevated in pancreatitis groups. H_2S addition was shown to decrease BAL LDH values significantly ($p<0.05$). In groups with pancreatitis, lung MDA and MPO values were significantly increased in non-pancreatitis groups ($p<0.05$). In the groupswith H_2S, lung MPO values were significantly decreased ($p<0.05$), although changes in MDA levels were not statistically significant. Previous studies showed that H_2S prevents lung injury induced by lipopolysaccharides (14, 37). H_2S was shown to decrease the number of free oxygen radicals in rabbits with lung transplantation (38).

Xu et al. (14) Showed that H_2S prevents lung injury, inhibits apoptosis and decreases inflammatory response in hemorrhagic shock-induced rats. Also, in a study by Liu et al. (39) it was reported that H_2S inhibits Fas pathway and has preventive effectsin acute lung injury-induced rats. In a study by Sidhapuriwala et al. (29) H_2S was shown to reduce lung MPO activity, pulmonary chemokines, and adhesion molecules.

Limitations

The present study had some limitations. Anti-inflammatory effects of H_2S are dose dependent and we only used 10 mg/kg. Studying a wider range of dose levels may providemore information about the effects of H_2S. Also, the effects of H_2S on inflammatory pathways of the other mediators except IL-6 were not evaluated.

CONCLUSION

In conclusion, autolysis of pancreas secondary to intraacinar enzyme activation is the most accepted theory in the pathogenesis of pancreatitis. Activation of leucocytes, released cytokines, and free oxygen radicals, resulting in multi-organ failure, is an important factor in pancreatitis progression. In the present study, we aimed to detect the dose-dependent effects of H_2S on rats with ANP. Although H_2S does have any effects on pancreatic necrosis, it decreases the mortality rates and improves organ functions. These are the dose-dependent partial anti-inflammatory effects of H_2S.

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Informed Consent: Not required in this study.

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Extralaryngeal division of the recurrent laryngeal nerve: A common and asymmetric anatomical variant

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ABSTRACT

Objective: Recognition of extralaryngeal branching of the recurrent laryngeal nerve is crucial because prevention of vocal cord paralysis requires preservation of all branches of the recurrent laryngeal nerve. We assessed the prevalence of extralaryngeal branching of the recurrent laryngeal nerve and the median branching distance from the point of bifurcation to the entry point of the nerve into the larynx.

Material and Methods: Prospective operative data on recurrent laryngeal nerve branching were collected from 94 patients who underwent thyroid or parathyroid surgery between September 2011 and May 2012.

Results: A total of 161 recurrent laryngeal nerves were examined (82 right, 79 left). Overall, 77 (47.8%) of 161 recurrent laryngeal nerves were bifurcated before entering the larynx. There were 36 (43.9%) branching nerves on the right and 41 (51.9%) branching nerves on the left, and there was no significant difference between the sides in terms of branching (p=0.471). Among 67 patients who underwent bilateral exploration, 28.4% were found to have bilateral branching, 40.3% had unilateral branching, and the remaining 31.3% had no branching. The median branching distance was 15 mm (5-60mm).

Conclusion: Extralaryngeal division of recurrent laryngeal nerve is a common and asymmetric anatomical variant. These variations can be easily recognized if the recurrent laryngeal nerve is identified at the level of the inferior thyroid artery and then dissected totally to the entry point of the larynx. Inadvertent division of a branch may lead to vocal cord palsy postoperatively, even when the surgeon believes the integrity of the nerve has been preserved.

Keywords: Thyroid surgery, anatomic variations, recurrent laryngeal nerve, laryngeal branches, vocal cord palsy

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INTRODUCTION

Thyroid surgery is a specific surgery that requires detailed anatomical information. The recurrent laryngeal nerve (RLN) is the major structure at risk during thyroid and parathyroid surgery (1). RLN paralysis is the most serious complication, along with postoperative hypocalcemia and hematoma, in thyroid surgery (2). Exploration and visual identification of the RLN is the gold standard method to preserve this nerve during thyroid surgery. Many factors have been reported to affect the development of RLN paralysis (2). One factor increasing the risk of RLN paralysis is anatomical variation of the RLN. Variations in the RLN can be produced by changes in the course of the nerve due to previous surgery or the impaction of a mass, the relationship between the RLN and inferior thyroid artery (ITA),the nonrecurrent laryngeal nerve course, and extralaryngeal branching (3, 4).

The relationship between the RLN and the ITA is variable. Makay et al. (5) defined 16 different relationships between the RLN and the ITA. Nonrecurrent laryngeal nerve course is a rare anatomic specialty. It is usually seen on the right side and arises during embryological development (6). Extralaryngeal branching of the RLN is a frequently seen anatomical specialty (3, 4). The risk of developing nerve paralysis is higher in extralaryngeal branching of the RLN (7, 8). The nerve may be vulnerable to compression, traction, and transection due to the diminished caliber of the nerve due to the branching (9). A wide range of branching rates have been reported in studies on branching of the RLN (4). We aimed to assess the prevalence of RLN branching, the median branching distance, and the symmetry of the nerve.

MATERIAL AND METHODS

The collected prospective data of 94 patients, including 165 neck sides, who underwent thyroid or parathyroid surgery in two surgeons' practices focused on endocrine surgery (MU, AI) between September 2011 and May 2012 were evaluated in this study. Each side of the operated neck was considered as a separate entity. One side of each of the four bilaterally explorated patients with diagnoses of primary hyperthyroidism was excluded from the study because the nerve was not followed until the larynx entry point. One hundred and sixty-one RLNs that were followed along their courses until the larynx entry point were included in the study.

This study was approved by the local ethics committee of our hospital. Written informed consent was obtained from all the patients.

Surgical Technique

While performing primary thyroidectomy and/or central neck dissection and bilateral parathyroid exploration, a 4-6 cm collar transverse incision was made. Superior and inferior subplatismal flaps were prepared, and the thyroid region was entered through the strap muscles. The area between the thyroid lobe and strap muscles was dissected, and the middle thyroid vein was taken.

After pulling the strap muscles laterally and the thyroid lobe anteromedially, the RLN was explored at the level of the medial section of the thyroid lobe where it crosses the ITA and followed until the laryngeal entry point under the cricopharyngeal muscle. The lateral approach was used for unilateral parathyroid exploration, revision thyroidectomy, and/or central neck dissection. After the dissection was performed through the anterior border of the sternocleidomastoid muscle and the lateral border of the strap muscles, the carotis sheath was found and the thyroid region was entered medially to the carotis artery. The RLN was explored and identified at the inferior section of the neck where it exits the thorax and was followed until the laryngeal nerve entry point (NEP) (10).

If the RLN had proximal branching before crossing the ITA, it was dissected until its branching point toward the inferior section in the medial approach. Therefore, the RLN was explored in the inferior section in the lateral approach, and the branchings proximally located to the ITA were already located in the dissection area; thus, there was no need for additional proximal dissection.

Any RLN branching was recorded. The distance between the point of bifurcation and the laryngeal NEP was measured in millimeters with a digital vernier caliper and defined as the branching distance. Only RLNs branching before entering the larynx at distances of 5 mm and greater were considered to be branched nerves; those branching in the last 5 mm were not categorized as branched because most RLNs branch in the last 5 mm before entering under the cricopharyngeal muscle (11, 12). Nerves with only posterior branches to the esophagus were not considered to be branching nerves. Nerves with two branches that both entered the larynx under the cricopharyngeal muscle were considered to be branching nerves (13, 14). It was found that some branching nerves bifurcated again from the anterior or posterior branches after the first bifurcation and entered the larynx as trifurcated nerves. This branching was defined as a secondary branching; details are provided in the results section.

At the end of each surgery, the demographic data of the patients, the indications for surgery, the surgical approach, and the anatomical data regarding the RLN were recorded in a Microsoft Excel table prepared at the beginning of the study.

Statistical Analyses

The data recorded in the Microsoft Excel table were used in the analyses. The descriptive statistics were given as number and percentage for categorical variables and mean value, standard deviation, and minimum and maximum values for numerical variables. The ratios of the categorical variables between the groups were analyzed by chi-square test. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

The median age of the 94 patients (76 females, 18 males) enrolled in this study was 44years (range 18-90 years). The indications for surgery and the surgical procedures are summarized in Table 1, 2 respectively.

Branching was detected in 77 of the 161 RLNs (82 right, 79 left) evaluated in the study. Seventy-two (93.5%) of 77 branching nerves had 2 branches, and the remaining 5 (6.5%) had 3 branches as a result of secondary branching when entering the larynx. Branching was detected in 36 (43.9%) of 82 nerves on the right side and 41 (51.9%) of 79 nerves on the left side. There was no significant difference in the branching rates between the sides (p=0.196). Three nerves on the right side (3.7% of the nerves on the right side and 8.3% of the branching nerves) and two nerves on the left side (2.5% of the nerves on the left side and 4.9% of the branching nerves) were seen to enter the larynx as three branches as a result of secondary branching. The secondary branchings were found on the anterior branches in two nerves (one right, one left) and on the posterior branches in three nerves (two right, one left).

Table 1. Indications for thyroid and/or parathyroid operations

Benign nodular goiter	MNG	25
	Recurrent goiter	4
	Solitary nodule	5
Fine needle aspiration biopsy	Bethesda III-IV	8
	Bethesda V	5
	Bethesda VI	7
Histopathologically diagnosed malignancy	Hyperthyroidism	3
	Toxic MNG	8
	Toxic adenoma	4
	Graves' disease	7
Hyperparathyroidism	HPT	14
	HPT+ MNG	2
	HPT+ papillary thyroid cancer	2

MNG: multinodular goiter; HPT: hyperparathyroidism

Table 2. Surgical interventions performed

Bilateral exploration	TT	46
	TT+CLND	10
	TT+PT	3
	BE+PT	7
	CLND	1
Unilateral exploration	L	19
	PT	7
	PT+L	1

TT: total thyroidectomy; BE: bilateral exploration; CLND: central lymph node dissection; PT: parathyroidectomy; L: thyroid lobectomy

Table 3. The branching properties of 161 nerves of 94 patients on the right and left sides

Bilateral exploration	Right branching+left non-branching	11
	Left branching+right non-branching	16
	Bilaterally branching	19
	Bilaterally non-branching	21
Unilateral exploration	Right side	
	Branching	6
	Non-branching	9
	Leftside	
	Branching	6
	Non-branching	6
Total		94

Table 4. The distribution of RLN branchings in patients who underwent bilateral intervention

	Right branching	Right non-branching	Total
Left branching	19 (28.4%)	16 (23.9%)	35
Left non-branching	11 (16.4%)	21 (31.3%)	32
Total	30	37	67

RLN: recurrent laryngeal nerve

19 (28.4%), 27 (40.3%), and 21 (31.4%) of 67 bilaterally explored patients had bilateral, unilateral, and non-branching nerves, respectively (Table 3, 4). The mean branching distance was 15 mm (range 5-60 mm).

If the right side was explored first in the bilaterally explored patients, the probability of detecting branching on the left side in the 30 patients with branched nerves was 63.6% (19 patients); in the 37 patients with non-branched nerves, the probability was 43.2% (16 patients). No significant difference was determined when comparing the probabilities of branching on the left side with branching or non-branching RLNs on the right side (p=0.082).

If the left side was explored first, the probability of detecting branching on the right side in the 35 patients with branched nerves was 54.3% (19 patients); in the 32 patients with non-branched nerves, the probability was 34.4% (11 patients). No significant difference was determined when comparing the probabilities of branching on the right side with branching or non-branching RLNs on the left side (p=0.082).

If branching was detected on the right or left side in the first exploration, no significant difference was determined when comparing the probabilities of identifying branching on the other side (p=0.314). If a non-branched nerve was detected in the first side exploration (right or left), no significant difference was determined when comparing the probabilities of identifying branching on the other side (p=0.307).

DISCUSSION

The RLN branches from the vagus nerve, which is located in the carotis sheath, at the thoracic inlet; it then courses up behind the subclavian artery on the right, curves up from the anterior to the posterior side of the aortic arch on the left, and enters the laryngeal entry point under the cricopharyngeal muscle. The right RLN enters the neck base more laterally than the left RLN because of its course around the right subclavian artery. Thus, the left RLN courses more strictly and closer to the trachea in the tracheoesophageal groove compared to the more oblique course in the paratracheal region on the right (15). The most important rule is that any tubular structure must not be divided unless the RLN is visually identified (10, 15). The RLN can be explored with three different approaches in the thyroid region: lateral, inferior, and superior (15). The lateral approach is the most commonly used approach for routine thyroidectomy. After traction of the strap muscles laterally and division of the middle thyroid vein, the thyroid lobe is retracted anteromedially at the midpolar level and the RLN is explored at the crossing point of the ITA and the RLN (10, 15). The RLN is found at the base of the neck in the inferior approach. The nerve is located more laterally on the right and in the paratracheal region on the left. The advantage of this approach, which is especially preferred for revision thyroidectomy, is that it allows the nerve to be explored in a loose areolar band atraumatically inferior to the previous surgical scar. In the superior approach, after the superior pole is dissected, the RLN is explored in the region of Berry's ligament where it enters the larynx. This approach can be used for large cervical and substernal goiters because this region is the most constant anatomic point for the RLN. Additionally, Berry's ligament is a fibrous structure and bleeds easily; thus, dissection is difficult in this area (15). Also, there may be branching in this area. It is important to remember that RLN injuries mostly occur close to Berry's ligament (4).

Extralaryngeal branching of the RLN is one of the most common anatomical variations (3, 4). Recognizing the branching and identifying all the branches of the RLN is an important factor in avoiding injury to the nerve. If a branched nerve is not detected, one of the identified branches can be considered as the main trunk. This situation may lead to inadvertent injury due to traction and division of the other branch (14). The most frequent cause of RLN paralysis is traction trauma. The power of traction due to traction of the thyroid lobe is reflected to the RLN in different proportions (16). Diminished diameter due to branching is an important risk factor for injury related to dissection and/or traction. The thinner nerve is more fragile and vulnerable to the maneuvers of routine dissection. The traction power over the branches is greatly diminished due to the decreased diameter and diminished coverage by tissues supporting the nerve, such as epineuria or fascia surrounding the nerve (9). The traction power upon the nerve is inversely proportional to the diameter of the nerve. The same traction causes greater tensile stress upon nerves with smaller diameters. The mean traction power that causes loss of the RLN signal detected by intraoperative neural monitoring can be calculated using the equation $\sigma=F/d^2$(σ: traction power upon the nerve; F: traction force applied during the loss of signal; d: diameter of the RLN) (17). For example, when the diameter of the nerve decreases from 2mm to 1mm, the same traction force applied to the 2 mm nerve reflects four fold on the 1 mm nerve. In other words, one fourth of a traction force that causes a loss of signal in the main trunk of a 2 mm nerve may cause a loss of signal in a branch of the same nerve that is 1mm in diameter. Serpell et al. (18) reported that although the same traction force was applied to each nerve in their study, which included unilateral interventions, the rate of RLN paralysis

on the left side was 2.7 times greater than that on the right side. They stated that a major factor was that the diameter of the nerve on the left (1.6 mm) was significantly thinner than that on the right (1.7 mm) (p=0.0012). Sancho et al. (8) found that the rate of vocal cord paralysis in branched nerves was two times greater thanthat in non-branched nerves (15.8% vs 8.1%, p=0.022). Also, the branching diameter was found to be significantly higher in paralyzed nerves than in functional nerves (29.4+10.4 mm vs 19.1+9.8 mm, p=0.003). Casella et al. (7) reported that the risk of RLN injury was 7 times greater for transient and 13 times greater for permanent unilateral paralysis in branched RLNs in comparison with non-branched RLNs after surgery. Branching of the RLN is reported in a wide range of 18.2%-72% in surgical series (3, 5, 7-9, 11-14, 18-23). The rate is reported to increase 92.7% in autopsy studies (24). Extralaryngeal branching is often seen as bifurcation, and the rate of branching greater than bifurcation is reported to be 1.4%-7.3% in the literature (3, 20, 23). The branching rate for more than two branches is 3.1%, similar to the literature. Many factors have been reported in the literature to affect the branching rates provided in studies. These factors have been reported as gender, right side, extension of surgical exploration, use of magnifying loops, altering of the branching diameter due to the surgical position of the patient, use of intraoperative neuromonitoring, and some defined exclusion criteria (3, 4, 7, 9, 12-14, 21, 25, 26).

Serpell et al. (12) and Randolph (15) have stated that they observed some small branches of the RLN going to the trachea, esophagus, or inferior constrictor muscle in 50%-60% of patients; the rate of real extralaryngeal branches entering the larynx is 20%-30%. The rates of extralaryngeal branching were reported as 64.5% and 72%, respectively, in studies by Cernea et al. (3) and Ardito et al. (20) in which more than 2000 RLNs were evaluated. All the branches of the RLN entering the larynx were evaluated in these studies. Katz (11) reported the rate of extralaryngeal branching as 58% in his study, in which he accepted branches before the 5 mm distance to the NEP. In the past ten years, the branching rate has been reported as 24%-43% in studies in which branchings were accepted if the RLNs were branched 5 mm or more below the NEP (12-14, 21). We determined the branching rate to be 47.8%, with 43.9% on the right and 51.9% on the left, in our study. It can be seen that although these rates are lower than those found by Katz (11), they are equal to or greater than the upper limit of the rates reported in recent studies. This high rate may be related to the surgical position of the patient. Kandil et al. (14) do not use a thyroid pillow to extend the neck; they reported branching distances of 7.5 mm on the right and 8.3 mm on the left. The median branching distance is 15 mm in our study, which is higher than these values. This high value may be related to our use of a thyroid pillow to extend the neck, leading to nerve stretching due to the position. The branchings within 5 mm that were not evaluated as real branchings in the study by Kandil et al. (13, 14) may have been evaluated as branching due to neck extension in our study. There is no data regarding the position of the patient in other studies. The gender and posture of the body also may affect the length of the nerve (13).

In our study, we detected bilateral branching in 28.4%, unilateral branching in 40.3%, and no branching in 31.4% of the bilaterally explored patients. This rate of bilateral branching is similar to the rate of 8.9%-33.3% that is reported in the literature (12, 13, 19, 22). In our study, if branching was observed in a patient, this branching was unilateral and asymmetric on the right or left at a rate of 58.9%. Gürleyik (19) reported the rate of unilateral branching as 71.4% in his study including 292 RLNs, in which the general branching rate was 31%. In their study, Serpell et al. (12) reported a rate of bilateral branching of 8.9% and a rate of unilateral branching of 77.9% in patients who underwent bilateral intervention. Serpell et al. (12) expressed that they always started from the left side while performing bilateral thyroidectomy. They found that when a branching nerve was detected on the left, the probability of finding a branching nerve on the right was 42.6%, and when a non-branching nerve was detected on the left, the probability of finding a branching nerve on the right was 24.3%. They reported that when a branching nerve was found on the left, the probability of finding a branching nerve on the other side was significantly high. Our preference is to start from the side with the pathological lesion when performing bilateral thyroidectomy. According to our data, when we started from the right and a branching nerve was found, the probability of finding a branching nerve on the left was 63.3%; however, if we started from the left and a branching nerve was found, the probability of finding a branching nerve on the right was 54.4%. If a non-branching nerve was found on the right, the probability of finding a branching nerve on the left was 43.2%, and if a non-branching nerve was found when starting from the left side, the probability of finding a branching nerve on the right was 34.4%. No significant difference was determined in terms of finding a branched nerve on the opposite side according to whether a branching or non-branching nerve was found on the first side explored. Also, the probabilities of finding a branching nerve on the opposite side were similar when branching and non-branching nerves were found on the first side (right or left). According to our data, when branching was present on the first side in bilaterally explored patients, a branching nerve was found on the opposite side in at least half the patients; if a non-branching nerve was found on the first side, branching was found on the opposite side in at least in one third of the patients. This is an important anatomical detail that should be considered in order to protect the RLN.

It is reported in some studies that branching is more frequent on the right side than on the left side (8, 21). Beneragama and Serpell (21) defined that the anatomic course of the RLN is different on the right and left, and the relationship with the ITA is more variable on the right. They stated that this embryological difference may be related to the increased frequency of RLN branching on the right. They found similar rates between the right and left sides in their subsequent extensive studies and stated that the observations obtained from more extensive series may be more reliable (12). The branching rates were found to be similar between the right and left sides in other studies (9, 13, 14, 18).

In some studies, it is suggested that the RLN should be explored on its last part around Berry's ligament before entering the larynx, and it is stated that early identification of RLN will not prevent its injury (25). The mean branching distance is reported as 6-19 mm in the literature (7-9, 12, 14). Gürleyik (19) divided the branchings into four classes on the basis of the points where they cross the ITA: 37.5% arterial, 32.5% postarterial, 15% prelaryngeal, and 15% prearterial. The median branching distance is 15 mm in our study, and the branching point is in the last 2-2.5 cm of the RLN where it crosses the ITA before entering the larynx. Partial exploration of the RLN

around Berry's ligament may cause many proximal branchings to be overlooked. Most branchings can be easily recognized by exploration of the RLN at the level of the ITA (4).

CONCLUSION

It is impossible to predict the branchings and other variations of the RLN preoperatively. The probability of branching of the RLN is high, and the branching is usually asymmetrical, with a unilateral rate of 60% in bilateral surgical approaches. When branching is present on the first explored side in bilaterally explored patients, branching is found on the opposite side in at least half of all cases; however, if there is no branching on the first side, branching is found on the opposite side in at least one third of all cases.Therefore, branching is an anatomical detail that should always be considered in the exploration of both sides. All the branches of the RLN must be set out to reduce the risk of injury, especially in the branching nerves, and save all the branches. The RLN must be explored in the region where it crosses the ITA, and all the branches must be followed until the nerve enters the larynx to mark all the branches clearly and save them. The injury of a nerve branch may unwittingly lead to vocal cord paralysis, although the surgeon may believe that the nerve was protected.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Şişli Etfal Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Contribution of intraoperative neuromonitoring to the identification of the external branch of superior laryngeal nerve

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ABSTRACT

Objective: We evaluated the contribution of intraoperative neuromonitoring to the visual and functional identification of the external branch of the superior laryngeal nerve.

Material and Methods: The prospectively collected data of patients who underwent thyroid surgery with intraoperative neuromonitoring for external branch of the superior laryngeal nerve exploration were assessed retrospectively. The surface endotracheal tube-based Medtronic NIM3 intraoperative neuromonitoring device was used. The external branch of the superior laryngeal nerve function was evaluated by the cricothyroid muscle twitch. In addition, contribution of external branch of the superior laryngeal nerve to the vocal cord adduction was evaluated using electromyographic records.

Results: The study included data of 126 (female, 103; male, 23) patients undergoing thyroid surgery, with a mean age of 46.2±12.2 years (range, 18-75 years), and 215 neck sides were assessed. Two hundred and one (93.5%) of 215 external branch of the superior laryngeal nerves were identified, of which 60 (27.9%) were identified visually before being stimulated with a monopolar stimulator probe. Eighty-nine (41.4%) external branch of the superior laryngeal nerves were identified visually after being identified with a probe. Although 52 (24.1%) external branch of the superior laryngeal nerves were identified with a probe, they were not visualized. Intraoperative neuromonitoring provided a significant contribution to visual ($p<0.001$) and functional ($p<0.001$) identification of external branch of the superior laryngeal nerves. Additionally, positive electromyographic responses were recorded from 160 external branch of the superior laryngeal nerves (74.4%).

Conclusion: Intraoperative neuromonitoring provides an important contribution to visual and functional identification of external branch of the superior laryngeal nerves. We believe that it can not be predicted whether the external branch of the superior laryngeal nerve is at risk or not and the nerve is often invisible; thus, intraoperative neuromonitoring may routinely be used in superior pole dissection. Glottic electromyography response obtained via external branch of the superior laryngeal nerve stimulation provides quantifiable information in addition to the simple visualization of the cricothyroid muscle twitch.

Keywords: Thyroidectomy, intraoperative neuromonitoring, external branch of the superior laryngeal nerve, nerve identification, cricothyroid muscle twitch

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INTRODUCTION

Voice impairments are common complaints after thyroidectomy. They are considered to be multifactorial in origin and can occur due to the trauma of neural or other laryngotracheal structures (1). The preservation of both the recurrent laryngeal nerve (RLN) and external branch of the superior laryngeal nerve (EBSLN) is necessary to maintain vocal cord function (2).

The superior laryngeal nerve is a branch of the vagus nerve near its exit from the jugular foramen of the skull base. It usually arises from the nodose ganglion of the vagus at the level of C2, about 4 cm cranially to the carotid artery bifurcation. In addition, it receives a branch from the superior cervical sympathetic ganglion.

About 1.5 cm caudally, the superior laryngeal nerve divides into a larger internal branch and a smaller external branch. The EBSLN descends dorsally to the carotid sheath and then crosses medially towards the larynx. The EBSLN has a course dorsal to the superior thyroid artery and superficial to the inferior pharyngeal constrictor muscle as it descends and runs medially to innervate the cricothyroid muscle (CTM) (3-5).

The CTM maintains the tension of the vocal folds during the production of high-pitched sounds (3). The position of EBSLN exposes it to the risk of injury during dissection of the superior thyroid pole. CTM paralysis caused by EBSLN injury does not enable the pitch elevation, which is particularly a great problem for women and voice professionals (4, 5).

Current prevalence of intraoperative injury of EBSLN has not been established in the literature so far because of the postoperative variability in voice symptoms and the difficulty of identifying the injury via the direct laryngoscopy and videostrobolaryngoscopy, compared with RLN injury (5). EBSLN injury rates have been reported to be approximately 58% (6). Thus, EBSLN injury is the most underestimated complication after thyroid surgery (5).

Several surgical techniques have been described to preserve EBSLN during the dissection of the superior thyroid pole, but none of them has been determined to be superior enough to decrease the potential risk of EBSLN injury (5). Intraoperative neuromonitoring (IONM) has gained widespread acceptance as an adjunct to the gold standard of visual identification of RLN (7). Routine identification of EBSLN was thought to be almost impossible and harmful to the nerve previously. However, IONM has recently been reported to be helpful and less invasive for identifying EBSLN (8-11). As these findings increased the surgical interest in using neuromonitoring for the identification of EBSLN, the rate of neuromonitoring use has increased over time. On an international survey in surgeons with known interest in thyroid surgery, the International Neural Monitoring Study Group in Thyroid and Parathyroid Surgery reported that IONM was used for the identification of the EBSLN by 26.3% of low-volume versus 68.4% of high-volume surgeons (p=0.004) worldwide, and 93% of respondents believed that EBSLN identification with IONM is necessary for voice professionals (12). We have been using IONM for EBSLN exploration since July 2012. In the current study, we aimed to evaluate the contribution of IONM to visual and functional identification of EBSLN.

MATERIAL AND METHODS

The prospectively collected data of 126 (female, 103; male, 23) patients undergoing thyroid surgery via IONM for the EBSLN exploration from January to December 2015 were assessed retrospectively. Each side of the neck was accepted as a separate entity, and 215 neck sides were assessed.

Patients were informed of the intent of using a monitoring system to potentially aid in avoiding any possible injury to RLN and EBSLN and assessing their functions during the operation. The patients provided written informed consent for the surgical procedure as well as the study and publication of the stored results according to the institutional review board. This study was approved by the hospital's Ethics Committee.

The exclusion criteria were revision surgery, thyroid cancer with massive extrathyroidal extension, intentional nerve transection because of cancer invasion, and failure to assess EBSLN function because of technical issues.

Medical records were collected and stored within a prospective database. The collected information included demographic features, indications for thyroid surgery, operative details (such as type of surgery and the IONM data) and postoperative period details.

Intraoperative Neuromonitoring Technique

The NIM-3.0 Neuro Monitoring System (Medtronic Xomed; Jacksonville, FL, USA) with endotracheal surface electrodes was adopted to test the nerve intraoperatively. The patient was under general anesthesia with a low-dose short-acting neuromuscular blockade (rocuronium 0.3 mg/kg) and intubated with Medtronic Xomed Nerve Integrity Monitor Standard Reinforced Electromyography Endotracheal Tube (size 6.0, 7.0, or 8.0 Fr). A sterile, single-use, pulse-generated monopolar stimulator probe (Medtronic Xomed; Jacksonville, FL, USA) was applied for nerve stimulation in the operative field with an interrupted stimulation technique, where in the probe was set to a value of 1 mA, impulse duration at 100 μs, frequency at 4 Hz, and the monitor was set for an event threshold of 100 μV. IONM setup, applications, and data interpretation were consistent with the International Neural Monitoring Guidelines (5, 7). The electromyographic waveform amplitude defined the vocal cord adductor function. Standard IONM was carried out as a 4-step procedure for RLN (V1, R1, R2, and V2). EBSLN function was evaluated via CTM twitch. An auditory signal and obvious glottis electromyographic waveform with EBSLN stimulation were also obtained in some cases and these electromyographic responses were recorded. Positive stimulation was defined as both the audible alarm of the monitoring system and achievement of a recognizable electromyographic waveform amplitude that was >100 μV, for both RLN and EBSLN.

Surgical Technique

Thyroidectomy and/or central neck dissection was performed by a 4-6-cm collar transverse incision. Subplatysmal flaps were raised, strap muscles were divided along the midline, the thyroid lobe was medialized, and middle thyroid vein was divided. A previously described systematic approach is used consistently for monitoring and identification of RLNs (13).

Superior thyroid pole dissection: Superior pole dissection was performed before or after lateral gland mobilization. The upper pole of the lobe was retracted laterally and caudally to expand the sternothyroid-laryngeal triangle (SLT). In cases of enlarged gland or short neck, the strap muscles were transected with ligasure (Covidien, Mansfield, MA) at one-third of superior edge with care to preserve the ansa cervicalis to provide a better exposure and dissection of the superior thyroid pedicle (5, 14).The avascular space between the superior pole and CTM was dissected bluntly for a better exposure of the SLT where the EBSLN lies. After the visual identification of EBSLN in the SLT, confirmation analysis with a monopolar stimulator probe via CTM twitch assessment was performed. If the EBSLN was not identified visually, it was searched with a stimulator probe under the laryngeal head of the sternothyroid muscle, which is a good landmark for the EBSLN's course, and followed over the inferior pharyngeal constrictor (IPC) muscle down towards the CTM (15). When EBSLN was not able to be identified using a probe, the fibers of IPC muscle were not dissected through to identify the nerve visually.

While managing the superior pole dissection, each portion of the pedicle tissue was stimulated with a probe to make sure that EBSLN is not trapped during the manipulations of the surgeon. After dividing the superior thyroid vessels, we stimulated EBSLN with a probe cranially to the division point of the vessels to confirm the integrity of EBSLN.

Evaluation of Vocal Cord Function

Patients underwent a routine pre- and postoperative (within 2 days) direct laryngoscopy, directed by an independent laryngol-

Table 1. Demographic profile, indications, and types of surgery

Variable	n
Gender (Female/Male)	103/23
Mean age (year±SD)	46.2±12.2
Range	(18-75)
Preoperative diagnosis	
Benign thyroid disease	83
euthyroid	65
hyperthyroid	18
Suspicious malignancy	21
Malignant	22
Procedure	
Bilateral approach	
TT	70
TT+CLND	15
TT+CLND+LND	4
Unilateral approach	
Lobectomy	37
EBSLNs at risk	215
RLNs at risk	215

SD: standard deviation; TT: total thyroidectomy; CLND: central lymph node dissection; LD: lateral dissection; RLN: recurrent laryngeal nerve; EBSLN: external branch of the superior laryngeal nerve

Table 2. The distribution of EBSLN identification methods

EBSLN identification methods	n (%)
Visual identification	
Direct visual identification	60 (27.9)
Visualization after identification with probe	89 (41.4)
Not visualized	
Identification with probe, (functional identification)	52 (24.1)
Total identification	201 (93.5)
Not identified	14 (6.5)
Total EBSLN at risk	(93.5)
EBSLN paresis (temporary)	3 (1.5)

EBSLN: external branch of the superior laryngeal nerve

ogist. RLN palsy was determined to be permanent when there was no evidence of recovery within 6 months after the surgery.

The visual identification rate of EBSLN and IONM's contribution to the visual and functional identification of EBSLN were evaluated.

Statistical Analyses

The incidence of nerve events was calculated based on the number of nerves at risk. Differences between continuous and categorical variables were assessed by the Mann-Whitney U test and Fisher's exact test or chi-square test, respectively. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

The study includes the data of 126 patients. Demographic characteristics, indication for surgery, and types of surgical procedures performed are presented in Table 1.

The methods used for EBSLN identification are described in Table 2. Two hundred and one (93.5%) of 215 EBSLNs were identified, but 14 (6.5%) EBSLNs were not able to be identified with IONM. Sixty (27.9%) EBSLNs were visually identified before being stimulated with a monopolar stimulator probe. Eighty-nine (41.4%) EBSLNs were visually identified after being stimulated with a probe. Although 52 (24.1%) EBSLNs were identified with a probe, they were not visualized. The IONM provided a significant contribution to visual ($p<0.001$) and functional ($p<0.001$) identification of EBSLN.

Additionally, positive electromyographic responses were recorded from 160 EBSLNs (74.4%). The amplitudes of the electromyographic waveforms obtained from RLNs and EBSLNs were 865±607μV (range, 311-2770) (Figure 1a) and 181±92μV (range, 100-392) (Figure 1b), respectively, with a significant difference when compared with each other ($p<0.001$). However, no CTM twitch was observed via stimulating the proximal parts of the three (1.5%) of 201 EBSLNs, although they were visually intact at the end of the surgery (Table 2). Voice changes were detected in three patients with identified EBSLNs, who had loss of signal on the proximal parts of EBSLNs at the end of their operations. Voice complaints of these three patients, such as inability to produce high-pitched sounds and vocal fatigue at the end of the day, improved within 4 months. There was no vocal cord paralysis in these patients.

All the vocal cord paralyses detected were unilateral. 11 (5.1%) temporary and 1 (0.5%) permanent RLN paralyses (RLNP) were detected.

DISCUSSION

External branch of the superior laryngeal nerve is in close relation with the superior thyroid vessels, causing it to be at risk during thyroid surgery. Various anatomical classification systems for EBSLN have been proposed including the Cernea, Friedman, and Kierner classifications (5). Cernea classification describes EBSLN to have three types with regard to its relation with superior thyroid vessels and superior thyroid pole.Type 1 EBSLN crosses the superior thyroid vessels more than 1 cm from the upper edge of the superior pole, while Type 2A nerve crosses the vessels less than 1 cm above the upper edge of the superior pole. Type 2B nerve crosses the superior thyroid vessels below the upper edge of the superior thyroid pole. This classification is the most widely accepted one that is based on the potential risk of injury to EBSLN during thyroid surgery (16). The rate of EBSLNs according to the Cernea classification has been reported in studies with results varying from 17% to 60% for Type 1, 17% to 59% for Type 2A, and 10% to 56% for Type 2B (4, 8, 9, 17, 18). The different results may be due to various factors such as, the race of the individual, height of the individual, weight of the thyroid gland, identification type of EBSLN (visually or with the use of IONM), and the extension of the study. Both Type 2A and 2B, but mostly Type 2B, EBSLNs

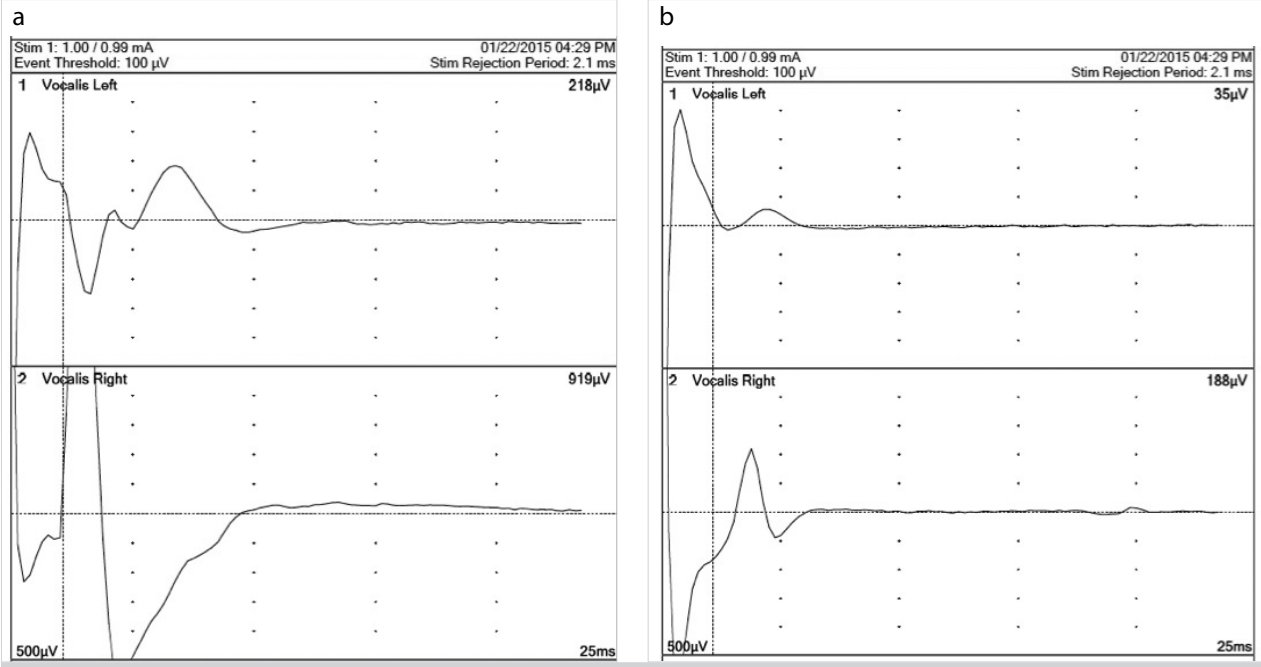

Figure 1. a, b. (a) The electromyographic waveform, with an amplitude of 919 µV, recorded from the right vocal cord via right RLN stimulation at the end of lobectomy. (b) The electromyographic waveform, with an amplitude of 188 µV, recorded from the right vocal cord via right EBSLN stimulation in the same patient

are at an increased risk of injury due to their close course to the superior thyroid vessels (4, 5).

Physical and functional preservation of EBSLN is as important as that of RLN and parathyroid glands for a safe thyroid surgery. Although the visual identification of RLN is accepted to be the gold standard to avoid injury, there is still no standard technique to preserve EBSLN and no consensus on the surgical protocol for EBSLN identification (19). Three techniques have been described to avoid EBSLN injury during the superior pole dissection. The first technique is the peripheral ligation of the individual branches of the superior thyroid vessels just on the thyroid capsule. The second technique is the visual nerve identification before ligating the vessels. The last one is the identification of the nerve with either a nerve stimulator or IONM before ligating the superior thyroid pole vessels (4, 5, 10, 20).

Some surgeons' expression that "I avoid injuring EBSLN by presuming where it should be, but I have never seen it" is not an appropriate approach for modern surgical principles. The fundamental principle of any surgery is the identification of a structure to avoid injuring it (21). Although nearly all RLNs can be visually identified, approximately 20% of the EBSLNs can not be visually identified due to their subfascial/intramuscular course into inferior constrictor muscle, which makes it necessary to conduct a microdissection for the identification of the nerve (22). Similarly, 25.2% of all the EBSLNs were identified with IONM, but all of them were not able to be visualized in the present study. In the present study, the visual identification rate of EBSLNs before being stimulated with a probe was only 27.9%, which was lower than the rate of 33%-93% reported in other studies (2, 10, 11, 17, 20). In our opinion, the reason for this low rate is that we did not divide the strap muscles to expose the sternothyroid-laryngeal triangle, except only in the patients with enlarged thyroid lobes and a short neck. EBSLN identification rate was 34.1% in another study similar to ours in which the sternothyroid muscles were not divided, but the rate was high as 80%-88% in other studies where the sternothyroid muscles were divided to improve visual control of EBSLN (8-10, 17). However, the visual identification rate of EBSLN increased to 68.3% with the aid of IONM, which is close to the rates reported in the studies that included the routine division of strap muscles during superior pole dissection. In this study, the functional identification rate of EBSLN with IONM was noted to be 93.5%, which is threefold of the visual identification rate and in accordance with the rate of 83%-100% reported in other studies (2, 8, 10, 11, 15, 23). We demonstrated that IONM provided a meaningful contribution to visual ($p<0.001$) and functional ($p<0.001$) identification of EBSLN. Additionally, it is also important to verify the visually identified structure by IONM because non-neural fibers or tendinous fibers of regional muscles can be confused for EBSLN (23). It is not always possible to identify EBSLN even for experienced thyroid surgeons. EBSLN is very fine, about 0.8 mm in diameter, and often invisible because of its course through the pharyngeal constrictor muscle (2). In cases in which surgeons cannot identify EBSLN, they can only assume that it is not injured with ligation of small portions of superior thyroid vessels (2).The widespread use of thermal sealing devices is another threatening factor for the preservation of the nerve (24). EBSLN's course can be only affirmed with the use of IONM (5, 10, 22).

The amplitude of the electromyographic waveform defined the adductor motor function of the vocal cords, whose main adductor is the thyroarytenoid muscle. In addition to the observed CTM twitch, electromyographic data could be achieved with EBSLN stimulation via the use of standard monitoring tubes in 70%-80% of cases (10, 25, 26). The distant most fibers of EBSLN penetrate the two heads of CTM extend-

ing to the anterior portion of thethyroarytenoid muscle and connect with RLN. This connection has been described as the "human communicating nerve" and is known to contribute to the motor innervation of the thyroarytenoid muscle (25, 27). The mean amplitude of EBSLN stimulation was significantly lower than that of RLN (10, 15, 25). Similar to these previous studies, we also achieved electromyographic responses from 74.4% of EBSLNs identified by IONM and the mean amplitude was 181±92 μV, which is lower than that of RLN (865±607 μV). Darr et al. (15) could find all EBSLNs and obtained recognizable electromyographic responses in 100% of cases via the use of a novel endotracheal tube having electrodes with an extended surface area, in their prospective study. They found that the electromyographic responses from the vocal cords had a great variability and tube position might influence the electromyographic waveform amplitudes. The mean electromyographic amplitudes were found to be similar between genders. Multiple nerve stimulations and extensive dissection did not affect EBSLN amplitude (15).

The reported prevalence of EBSLN injury alters widely from 0% to 58% (4, 6, 8, 10, 28). It is difficult to evaluate the actual prevalence due to the limited data, difficulty of quantifying EBSLN function, and differences in diagnostic techniques in various studies. CTM electromyography is the only definitive way to detect EBSLN injury because of the variability in vocal symptoms and findings at the postoperative laryngeal examination (5). Electromyography of CTM is too invasive to perform routinely and can be difficult to comment on secondary to variability in electromyographic needle placement. It is, therefore, very important to confirm that EBSLN is preserved during thyroidectomy by IONM (2).

Limitations of the Study

The present study has several limitations. First, the study is a retrospective one, although the data were collected prospectively. The patients without vocal cord paralysis and loss of signal in EBSLNs did not have voice change complaints. All three patients with identified EBSLNs via IONM had loss of signal on the proximal parts of EBSLNs after the dissection, supporting the fact that the voice change complaints were due to EBSLN injury. The voice change complaints of the patients were all temporary. However, one of the major limitations is that we could not evaluate the exact prevalence of EBSLN injuries in the patients postoperatively by electromyography. It is not a practical method to apply to all the patients who undergo thyroidectomies.

CONCLUSION

As a conclusion, IONM provides a significant contribution to the preservation of EBSLN by improving both the visual and functional identification of it. We think that EBSLN risk is unpredictable and IONM should be used in the superior pole dissection routinely. Although EBSLN's main function is to innervate CTM, it also contributes to the vocal cord's adductor function due to the presence of communicating nerves between RLN and EBSLN. Thus, glottis electromyographic response obtained with EBSLN stimulation provides quantifiable information in addition to the simple visualization of CTM twitch.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Şişli Hamidiye Etfal Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Course of sepsis in rats with thyroid dysfunction

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ABSTRACT

Objective: Numerous studies show the relationship between sepsis and thyroid hormones. Virtually all these studies investigate changes in post-sepsis thyroid hormones and the relationship between these changes and the progression of the disease. Our aim in this study was to investigate the progression of sepsis in rats with thyroid dysfunction.

Material and Methods: The study involved four groups, each containing seven female Wistar albino rats: Group 1: Sham, Group 2: Control (Sepsis), Group 3: Hyperthyroidism-Sepsis, and Group 4: Hypothyroidism-Sepsis. Group 1 only received laparotomy. Group 2 only had sepsis. Sepsis was induced in Group 3 and Group 4 following formation of hyperthyroidism and hypothyroidism, respectively. After 24 hours, relaparotomy and thoracotomy were performed, and tissue and blood samples were drawn.

Results: Dysfunctions seen in the liver, lungs, and kidneys during sepsis and other findings of sepsis were milder in the hyperthyroidism group in comparison to both the control and hypothyroidism groups.

Conclusion: The results of Simon's grade, histopathological organ damage, and laboratory parameters revealed that the progression of sepsis was milder in the hyperthyroid group than in the hypothyroid and euthyroid groups. The progression in the hypothyroid group was the most severe. Therefore, the results of the study raise the question of whether immediate treatment in cases of hypothyroidism and slow return of thyroid function to normal levels in cases of hyperthyroidism are adequate treatment approaches in patients who may develop sepsis or septic shock." To determine the answer to this question, more detailed studies are required with a higher number of subjects.

Keywords: Hyperthyroidism, hypothyroidism, organ dysfunction, sepsis

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INTRODUCTION

Critical diseases cause hormonal changes that may vary during the acute and chronic phases of the disease (1). Changes are also seen during disease along the hypothalamic-pituitary-thyroid (HPT) axis. These changes are typically related to a decrease in the total 3, 5, 3′-L-triiodothyronine (T3) level. The term non-thyroidal illness syndrome (NTIS) is used to describe the changes in thyroid-related hormone levels during acute or chronic illness (2). Decrease in T3 is the most common finding in NTIS. The only finding may be decreased T3 levels in diseases with relatively mild progression. As the severity of disease increases, decreases in 3, 5, 3′-L-tetraiodothyronine (T4) and thyroid stimulant hormone (TSH) levels along with T3 and elevation of reverse T3 level are seen (3). Some studies have linked this change in thyroid hormones during sepsis and septic shock with poor prognosis (4). Studies demonstrating the relationship between relative hypothyroidism and poor prognosis have focused on thyroid hormone treatment during sepsis.

Numerous studies in the literature show a relationship between sepsis and thyroid hormones. Virtually all these studies investigated changes in post-sepsis thyroid hormones and the relationship between these changes and the progression of the disease. However, in this study, we aimed to investigate the progression of sepsis in rats with previous conditions of hyperthyroidism or hypothyroidism.

MATERIAL AND METHODS

This study was approved by Necmettin Erbakan University KONUDAM Experimental Medicine Research and Study Center's local ethics board for animal trials on 11.14.2014 (decree 2014-056); all institutional and national guidelines for the care and use of laboratory animals were followed. The study was conducted at Necmettin Erbakan University KONUDAM Experimental Medicine Research and Study Center. All procedures related to animals were performed in adherence to the Strasbourg Contract (ETS 123 and ETS 170) and Directive 2010/63/Eu of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Twenty-eight female Wistar albino rats weighing 260 to 320 grams were used in the study. Four groups, each containing seven animals, were formed. Group 1 was designated as the sham group, while Group 2 was the control sepsis group, Group 3 was the hyperthyroidism + sepsis group, and Group 4 was the hypothyroidism + sepsis group. All animals were fed with standard feed and water for 15 days. Before the experiment, the rats were housed in wire cages at a temperature of 22°C and 50% to 60% humidity with 12 hours night, 12 hours day circadian rhythms. A maximum of five rats were housed in a single cage. Solid foods were removed from the rats' diet 12 hours before surgical procedures, and water was removed 2 hours prior to surgery. The rats in

Group 3 were administered a daily dose of 250 µg/kg L-thyroxine (Sigma) dissolved in 0.1 N NaOH and diluted with normal saline intraperitoneally (i.p.) for 15 days; thus, hyperthyroidism was established (5). The animals in Group 4 were i.p. injected with 0.5 ml 6-n-propyl-2-thiouracil (Sigma) dissolved in isotonic solution for 15 days at a daily dose of 10 mg/kg (6). Before the surgical procedures, all animals were anesthetized with 50 mg/kg ketamine HCl and 15 mg/kg xylazine subcutaneously. Following anesthesia, at the end of the 15th day, all the rats underwent mini-laparotomy operations with a midline incision. The rats in the sham group did not undergo further procedures; their abdomens were closed in two layers with 4/0 silk after their cecae were isolated. Experimental sepsis formed in the other groups (groups 2, 3, and 4) in line with the cecal ligation and perforation (CLP) model (7) (Figure 1). To achieve this, the cecum was isolated; after the visible colon was patted and filled with feces, it was ligated with 3/0 silk below the iliocecal valve; the cecum was perforated with an 18-gauge branule needle, and the abdomen was continuously closed in two layers with 4/0 silk. After the procedure, a 2 mg/mL dose of paracetamol tablets was mixed in drinking water to provide analgesia. At the end of 24 hours, anesthesia was performed in the same way; all rats underwent relaparatomy and thoracotomy, and intraabdominal inflammation was graded according to Simon's method (8) (Table 1). Intracardiac blood was drawn for biochemical and hormonal analyses. Tissue samples from the liver, lungs, and kidneys were acquired for pathological diagnoses. The animals were euthanized under anesthesia by exsanguination.

Renal function tests (urea, creatinine), hepatic function tests (AST, ALT), C-reactive protein (CRP), thyroid tests (fT3, fT4, TSH), and blood gas parameters (pH, pCO_2, pO_2, lactate, SaO_2, HCO_3) were analyzed in the drawn blood. The following were evaluated under a light microscope by a pathologist who had no knowledge of the groups: in liver specimens: inflammation, congestion, Kupffer cell hyperplasia, and hydropic degeneration; in lung specimens: inflammation, congestion, and atelectasis; in kidney specimens: inflammation, congestion, and tubular cell degeneration.

Statistical Analysis

The statistical analysis of the collected data was conducted using the Statistical Package for the Social Sciences (IBM Corp.; Armonk, NY, USA) 20.0 software package. When parametric conditions were met for intergroup comparisons, one-way analysis of variance (ANOVA) was used, while Kruskal-Wallis variance analysis was implemented for other cases. For binary comparisons, the post-hoc Tukey test was preferred. For the comparison of two groups, Student's t-test or the Mann-Whitney U test was used. To determine whether categorical variables were related, chi-square analysis was used; to pinpoint the relationships between numeric variables, Pearson's and Spearman's correlation tests were used. $P<0.05$ was regarded to be statistically significant for all analyses.

RESULTS

One rat from the hypothyroidism group died 18 hours after implementation of the sepsis model in the course of the study. This rat underwent relaparotomy and thoracotomy immediately after mortality. Following the grading of intraabdominal sepsis according to Simon's method, tissue samples were taken. Because no blood samples could be drawn from this rat, the laboratory parameters were evaluated over six rats in this group.

24 hours after completion of the CLP procedure, it was seen that clinical findings such as coarsening of the hair, slower motion, reluctance to feed, and somnolence became more prominent, especially in the hypothyroidism and control sepsis groups.

With respect to Simon's grade, the hyperthyroidism group had a more moderate outlook than the control sepsis group. The results of the hypothyroidism group, however, were poorer than those of the other three groups (Table 2, Figure 2). Among the clinical parameters, Simon's grade had negative correlations with fT3 ($p=0.029$) and fT4 ($p=0.004$); however, no correlations were seen with regard to TSH level ($p=0.268$).

fT3 ($p=0.002$), fT4 ($p=0.016$), and TSH ($p<0.001$) levels were found to be significantly different in all groups (Table 3). The fT3 level was the highest in the sham group and was the lowest in the hypothyroidism group. Binary group comparisons of the fT4 levels demonstrated that the hormone level was significantly lower only in the hypothyroidism group than in the sham group ($p=0.013$). TSH levels were found to be highest in the hypothyroidism group.

Binary group comparisons of the neutrophil counts revealed that the sham group was not statistically significantly different from the hyperthyroidism group ($p=0.121$); in contrast, the results in hypothyroid group were the poorest (Table 3). While pH levels were statistically lower in the hypothyroidism and control sepsis groups than in the sham group ($p=0.049$ and $p=0.035$, respectively), the results of the sham group and the hyperthyroidism group were not significantly different ($p=0.953$). pCO_2 levels were found to be higher in the control sepsis group ($p=0.027$) and the hypothyroidism group ($p=0.017$) than in the sham group, whereas the results of the hyperthyroidism group ($p=0.978$) and the sham group were not statistically significantly different (Table 3). AST, ALT, and CRP were also significantly higher in the hyperthyroidism and hypothyroidism groups than in the sham group ($p<0.005$).

When the organ damage was histopathologically evaluated, liver, lung, and kidney damage were most severe in the hypothyroidism group, followed by the control sepsis group. The results of the hyperthyroidism group were better than both groups (Table 4, Figure 3-5). Also, there was a negative correlation between hepatic and renal failure and fT3 level ($p<0.005$).

DISCUSSION

Sepsis is described as a systemic disease condition brought about by microbial invasion of normally sterile areas of the body. Sepsis conditions accompanied by hypoperfusion and at least one organ dysfunction are called severe sepsis; if vasopressor need or hypotension, which are seen during adequate fluid resuscitation, is added to severe sepsis, it is called septic shock (9). The results of our study showed that the disease was less severe in the hy-

Table 1. Classification of peritoneal inflammation according to Simon's method

Grade 0	No inflammation
Grade 1	Well-walled-off abscess, no free peritoneal fluid
Grade 2	Walled-off abscess, small amount of free peritoneal fluid, and patchy areas of cecal wall necrosis
Grade 3	Poor localization of the inflammatory process, moderate amount of free peritoneal fluid, and gangrenous cecum
Grade 4	No walling off of the cecum, large amount of free hemorrhagic fluid in the peritoneal cavity, and extensive gangrene and hemorrhagic fluid in the cecal wall

perthyroidism group than in both the hypothyroidism and the control sepsis groups. Moreover, not only laboratory parameters, but also histopathological symptoms referring to liver, lung, and kidney damage were better in the hyperthyroidism group than in either the control sepsis or hypothyroidism groups.

Among the inflammatory molecules secreted by the host and used for the diagnosis of infection, the presence of bacteremia, and the progress and mortality of disease are TNF-α, IL 6, CRP, and procalcitonin, which is recently being used more frequently (10). Thyroid hormones are a point of interest in this regard. Decrease in T3 is the most frequently seen finding; it may be the only finding in T3 in diseases with milder progression. As the severity of the disease increases, T4 and TSH levels decrease along with T3, and an increase in reverse T3 level is observed (3). In our study, we concluded that fT3 and fT4 levels were lowest in the hypothyroidism group, followed by the control sepsis, hyperthyroidism, and sham groups. In contrast, the TSH level was significantly higher in the hypothyroidism group. This situation was related to the antithyroid treatment administered before the CLP procedure.

Recent studies have argued that low thyroid hormone levels are signifiers of poor outcomes in sepsis (11). The results of a review study conducted by Angelousi et al. (4), which examined nine studies on the subject, revealed that six of nine studies demonstrated significantly lower total or free T3 and T4 levels in deteriorating septic patients than in other patients. In another study by Sharma et al. (12) investigating the relationship between thyroid hormone dysfunction and CRP levels during sepsis in newborns, the authors demonstrated a close relation-

Figure 1. Cecal ligation and perforation

Table 2. The distribution of Simon's grades according to the groups

Simon's grade	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=7)	Group 4 (n=7)
Grade 0	7	-	-	-
Grade 1	-	-	-	-
Grade 2	-	2	4	2
Grade 3	-	4	3	2
Grade 4	-	1	-	3

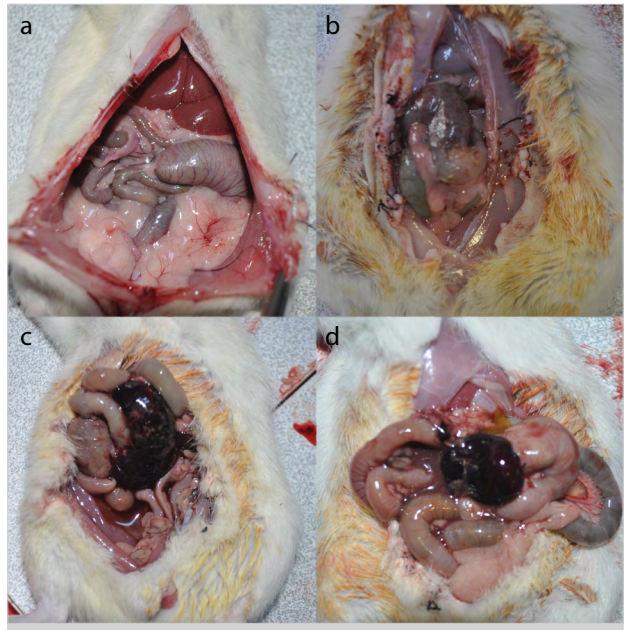

Figure 2. a-d. Simon's grades. Grade 0 (an animal from the sham group) (a). Grade 2 (an animal from the hyperthyroidism group) (b). Grade 3 (an animal from the control sepsis group) (c). Grade 4 (an animal from the hypothyroidism group) (d)

Table 3. Blood sample results

Blood parameter	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=7)	Group 4 (n=6)	p
fT3 (pg/mL)	2.27±0.38	1.52±0.35	2.21±0.54	1.49±0.38	0.002
fT4 (ng/dL)	1.07±0.10	0.69±0.22	0.80±0.34	0.56±0.36	0.016
TSH (μIU/mL)	0.47±0.18	0.40±0.29	0.33±0.25	2.53±0.52	<0.001
Neutrophils	2.7±0.77	7.77±3.43	5.80±1.56	8.50±3.30	0.001
pH	7.33±0.7	7.21±0.09	7.31±0.80	7.21±0.62	0.013
pCO_2 (mmHg)	44.24±10.60	58.82±5.51	46.15±9.62	60.43±9.33	0.004
AST (u/L)	152.57±61.61	287.71±97.36	314.14±116.00	358.33±87.59	0.03
ALT (u/L)	65.57±22.26	163.28±62.94	230.14±86.40	237.16±43.27	<0.001
Urea (mg/dL)	31.77±7.31	88.24±35.41	119.92±34.68	122.86±44.65	<0.001
CRP (mg/L)	1.04±0.59	3.91±1.54	3.71±1.73	4.24±1.72	0.02

TSH: hyroid stimulant hormone; AST-ALT:hepatic function tests; CRP: C-reactive protein

Table 4. Histopathological findings in the liver, lung and kidney

Tissue samples	Histopathological findings		Grup 1 (n=7)	Grup2 (n=7)	Grup 3 (n=7)	Grup 4 (n=7)
Liver	Inflammatory cell infiltration	0	7	2	7	1
		1+	-	4	-	3
		2+	-	1	-	3
		3+	-	-	-	-
	Congestion	0	2	-	5	-
		1+	5	1	2	-
		2+	-	6	-	5
		3+	-	-	-	2
	Kupffer cell hyperplasia	0	7	7	7	7
		1+	-	-	-	-
		2+	-	-	-	-
		3+	-	-	-	-
	Hydropic degeneration	0	7	7	7	7
		1+	-	-	-	-
		2+	-	-	-	-
		3+	-	-	-	-
Lung	Inflammatory cell infiltration	0	7	-	-	-
		1+	-	-	-	-
		2+	-	4	4	4
		3+	-	3	3	3
	Congestion	0	3	-	-	-
		1+	4	-	-	-
		2+	-	5	6	2
		3+	-	2	1	5
	Atelectasis	0	2	-	-	-
		1+	5	-	1	-
		2+	-	4	2	3
		3+	-	3	4	4
Kidney	Inflammatory cell infiltration	0	7	5	7	4
		1+	-	2	-	3
		2+	-	-	-	-
		3+	-	-	-	-
	Congestion	0	4	-	4	-
		1+	3	2	3	-
		2+	-	5	-	6
		3+	-	-	-	1
	Tubular cell degeneration	0	7	-	2	-
		1+	-	3	5	6
		2+	-	4	-	1
		3+	-	-	-	-

ship between low fT3 level and high CRP level. Furthermore, Wang et al. (13) proved that fT3 was related to intensive care mortality in a prospective study that compared intensive care mortality and thyroid function. Numerous studies have been conducted, in addition to those mentioned above, on the relationship between thyroid hormones and the progression of sepsis. These studies reveal conflicting results regarding whether changes in thyroid hormones are related to the progression of sepsis, whether these changes are signifiers of mortality, and which thyroid hormones are better signifiers. The main cause of these inconsistencies is that almost all these studies were observational ones conducted with adult or pediatric intensive care patients. Therefore, it is not known whether the patients in the studies had previous conditions of underlying thyroid disease. Most drugs used in intensive care (such as dopaminergic agents) may lead to thyroid dysfunction; some studies did not exclude patients receiving these drugs. Most of the patients had comorbid diseases that could affect thyroid functions; these patients were not excluded in some studies. In contrast, in our study, we addressed the problems that limit the dependability of some previous studies; also, the relationship between thyroid hormone levels and the progression of sepsis was evaluated in a reliable manner. According to the data we collected, there were

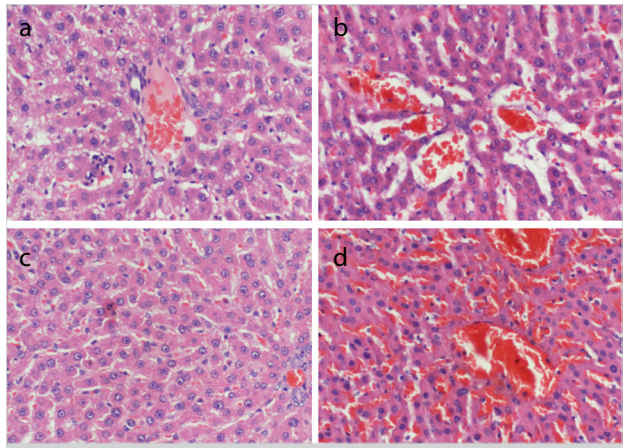

Figure 3. a-d. Hepatic tissue (H&E ×200). Sample from the sham group (histopathologically normal outlook) (a). Sample from the control sepsis group (pronounced congestion and sporadic inflammatory cell infiltration) (b). Sample from the hyperthyroidism group (histopathologically normal outlook) (c). Sample from the hypothyroidism group (advanced congestion and inflammatory cell infiltration) (d)

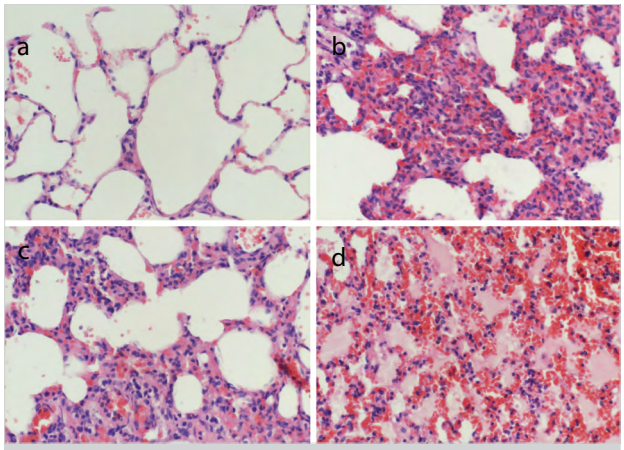

Figure 4. a-d. Lung tissue (H&E -200). Sample from the sham group (histopathologically normal outlook) (a). Sample from the control sepsis group (extensive inflammatory cell infiltration, congestion, and atelectasis areas) (b). Sample from the hyperthyroidism group (inflammatory cell infiltration, mild atelectasis, and congestion areas) (c). Sample from the hypothyroidism group (advanced congestion, pronounced atelectasis areas, and inflammatory cell infiltration accompanied by plasma cell infiltration in the alveoli) (d)

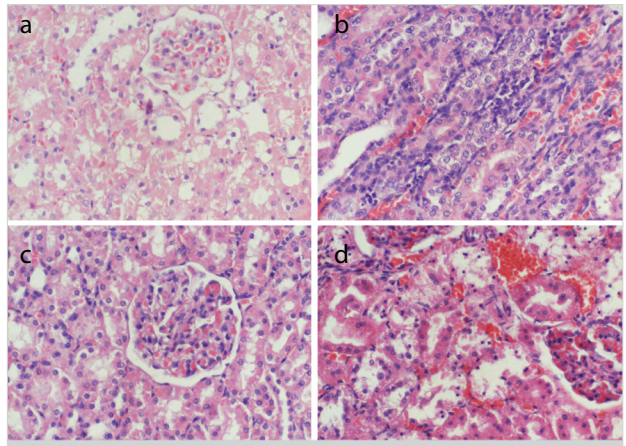

Figure 5. a-d. Kidney tissue (H&E ×200). Sample from the sham group (histopathologically normal outlook) (a). Sample from the control sepsis group (sporadic inflammatory cell infiltration, congestion, and pronounced tubule cell degeneration) (b). Sample from the hyperthyroidism group (histopathologically normal outlook) (c). Sample from the hypothyroidism group (pronounced congestion and tubule cell degeneration) (d)

negative correlations between the clinical phase of the disease and fT3 (p=0.029) and fT4 (p=0.004) levels; however, no correlations were seen with regard to TSH level (p=0.268). There was a negative correlation between hepatic and renal failure and fT3 level (p<0.005). In light of these data, it was concluded that fT3 is a more valuable parameter in demonstrating damage, especially histopathological damage.

CONCLUSION

Simon's grade, histopathological organ damage, and laboratory parameter results revealed that progression of sepsis was less severe in the hyperthyroid group than in the hypothyroid and euthyroid groups. The progression of sepsis was most severe in the hypothyroid group. Therefore, the results of this study raise the question of whether immediate treatment in cases of hypothyroidism and slow return of thyroid function to normal levels in cases of hyperthyroidism are adequate treatment approaches in patients who may develop sepsis or septic shock." To determine the answer to this question, more detailed studies with a higher number of subjects are necessary.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University KONUDAM Experimental Medicine Research and Study Center's (date: 11.14.2014/decision no: 2014-056).

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

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Prognostic value of E2F1 in rectal cancer

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ABSTRACT

Objective: To evaluate whether E2F transcription factor 1 is a potential prognostic marker in patients with rectal cancer.

Material and Methods: Eighty-two patients who were treated with curative resection because of rectal cancer in the Erciyes University School of Medicine, Department of General Surgery were included in the study and analyzed retrospectively. Data were obtained from patient files, pathology reports, and hospital information system. Nuclear and cytoplasmic staining of E2F transcription factor 1 was performed for immunohistochemical analysis on paraffin-embedded and blocked tumor tissue samples of patients. The findings of the study were assessed with using IBM Statistical Package for Social Sciences Statistics 20.

Result: In the 5-year follow-up period, 34 (41.5%) patients were alive. Local recurrence was identified in 7 patients. According to E2F transcription factor 1 nuclear staining, the average survival rate in patients was 60% for strong nuclear staining and 28% for weak nuclear staining. There was significant statistical difference between groups according to their degree of nuclear staining (p=0.017). When the patients were evaluated according to cytoplasmic staining with E2F transcription factor 1, the average overall survival rate of patients with positive E2F transcription factor 1 cytoplasmic staining was 48.0±4.6% versus 55.9±7.9% for patients without staining (p=0.408).

Conclusion: The survival rates are higher in rectal cancer patients with strong immunohistochemical nuclear staining of E2F transcription factor 1.

Keywords: Rectal cancer, E2F1, prognosis

INTRODUCTION

Colorectal cancers constitute approximately 10% of all cancer cases (1). Almost 1,000,000 patients are diagnosed with colorectal cancer worldwide each year, and almost 500,000 people die from this disease annually. Colorectal cancer is the third most common type of cancer in both sexes; it is the second most common cause of death due to cancer in men and the third most common cause of death due to cancer in women (2). Although developments in both the surgical and oncological treatment methods of patients with colorectal cancer make a positive contribution to the survival of patients, the lack of prognostic parameters to predict the effectiveness of treatment planning is still a major problem.

E2F transcription factor 1 (E2F1) is a transcription factor that both activates and suppresses many biological processes such as DNA replication, mitosis, DNA repair, differentiation, and autophagy. It can also trigger apoptosis (3, 4). Disruption of various parts of the pathway that controls the growth of E2F1 molecules leads to loss of control and the development of a variety of cancers (5-7). It has been shown that E2F1 plays a role in thyroid and non-small-cell lung carcinomas and the expression of E2F1 induces medulloblastoma, glioma and lung, colon, and bladder cancers after treatment with adriamycin or etoposide (8-12). It was reported that E2F1 has a higher ratio of nuclear positivity and is associated with aggressive behavior in malignant gastrointestinal stromal tumors (13).

Additionally, E2F1 has been studied a prognostic marker in gastric, urothelial carcinoma of urinary bladder, and squamous cell carcinoma of the tongue; however, it has been not previously studied in rectal cancers (14-16). The purpose of this study was to investigate whether E2F1 is a potential prognostic marker in the diagnosis of rectal cancer patients who undergo curative surgery.

MATERIAL AND METHODS

After receiving ethical approval, the study was performed jointly by the Erciyes University School of Medicine, Department of Pathology. Eighty-two patients who were treated with curative resection due to rectal cancer at the Erciyes University School of Medicine, Department of General Surgery were included in the study. Informed consent was obtained from all patients before surgery. The names and

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surnames of the patients; hospital protocol numbers; age; gender; address; telephone number; and identifying information, such as data on demographic characteristics, dates of surgery, the operation and perioperative period information (such as local recurrence, tumor histological type, differentiation, tumor size, the number of lymph nodes affected, the involvement of local invasion, vascular invasion, perineural invasion, and positive surgical margins) were obtained from patient files, hospital information system, and pathology reports. The data were analyzed retrospectively.

The current condition of the surviving patients was determined according to the findings of the last follow-up. The final status of the population whose last follow-up date was more than 6 months before were investigated by telephone or from the population directorate. Staging was done according to the criteria of the American Joint Committee on Cancer (AJCC) 2010 staging of colon and rectal cancer. All tissue samples were taken from surgical excision materials. Paraffin-blocked tissue samples of patients were obtained from the archives of the Department of Pathology.

Immunohistochemical Staining of E2F1

Tissue sections of the 82 patients' formalin-fixed 5-6-micron paraffin blocks were transferred to poly-L-lysine coated slides for immunohistochemical studies. The tissue sections were deparaffinized with xylol after standing for an hour in the incubator and then dehydrated with alcohols in rising degree (4 times for 2 min). Endogenous peroxidase activity was blocked with hydrogen peroxide. Tissues were heated with Ethylenediaminetetraacetic acid (EDTA) buffer in the microwave 3 times for 10 min and then allowed to cool for 5 min. The tissues were washed with phosphate buffered saline (PBS). E2F1 antibody (Santa Cruz Biotechnology, USA, dilution 1:100, incubation time 30 min) was added and allowed to stand in the refrigerator overnight. In the next step, the tissues were washed with tris-buffered saline (TBS, pH=7.4). Antigen-antibody binding was made visible by being incubated with biotinylated anti-rabbit antibody, streptavidin, Avidin-Biotin Complex (ABC) with Horseradish Peroxidase (HRP) solution, and diaminobenzidine for 10 min, in that order. They were counterstained with hematoxylin (Mayer). Then, the washed preparations were closed with a coverslip instilled with balsam.

Immunohistochemical Evaluation of E2F1

For the positive control, internal staining of the tissue was evaluated for immunohistochemical staining. Tonsil tissue was used as a positive control. For the nuclear staining of E2F1, 500 cells were counted under 10× magnification and were classified as mild, moderate, and severe according to the severity of staining (Figure 1).

Statistical Analysis

Data were evaluated with the IBM Statistical Package for the Social Sciences 20 statistical package program (IBM Corp.; Armonk, NY, USA). The mean, percentage, and standard deviation were given as descriptive statistics. Quantitative variables were compared with the normal distribution of the Shapiro-Wilk test. Comparisons between groups according to the normality of variables were done with Student's t-test and Kruskal-Wallis tests. The exact method of the Chi-square test was used to compare categorical variables. Disease-free and overall survival were assessed using Kaplan-Meier survival analysis and the log-rank test. To determine the factors that influence disease-free and overall survival, Cox regression analysis was used. A p value of <0.05 was considered statistically significant.

RESULTS

Fifty-three patients (64.6%) were male and 29 (35.4%) were female. The mean age was 68.1±1.5 years and the median age was 69 (33-82). The histopathological features of the patients are shown in Table 1 and the surgical methods are shown in Table 2.

In terms of nuclear immunohistochemical staining of E2F1, 7 cases (8.5%) showed strong staining, 17 cases (20.7%) showed weak staining, and 58 cases (70.7%) showed no staining. When the same cases were evaluated according to whether they

Table 1. The histopathological features of the patients

Histology	**N**	**%**
Adenocarcinoma	79	96.3
Other	3	3.7
Invasion		
Serosa	53	64.6
M. Propria	21	25.6
Subserosa	4	4.9
Adipose Tissue	2	2.5
Mucosa	1	1.2
Submucosa	1	1.2
Vascular Invasion		
Yes	25	30.4
No	57	69.6
Perineural Invasion		
Yes	18	22
No	64	78
Surgical Margin		
Positive	3	3.6
Negative	79	96.4
Lymph Node Metastasis		
Yes	33	40.2
No	49	59.8

Table 2. The surgical methods

	N	**%**
LAR	32	39
APR	29	35.4
Anterior Resection	17	20.7
Total Colectomy	4	4.9
Total	N=82	

LAR: low anterior resection; APR: abdominoperineal resection

were stained or unstained, 24 cases (29.3%) were stained and 58 (70.7%) were unstained.

In terms of cytoplasmic immunohistochemical staining of E2F1, it was observed that 11 cases (13.4%) were strongly stained, 28 (34.1%) were moderately stained, 19 (23.2%) were weakly stained, and 24 (29.3%) were unstained. When the same patients were grouped according to whether there was staining or not, 58 cases (70.7%) were stained and 24 cases (29.3%) were unstained. In a 5-year follow-up, 34 patients (41.5%) were alive and 7 (0.9%) patients had local recurrence. The average 5-year survival was 43.7±3.4 months.

Survival rates were compared across different time periods depending on the staining of the nucleus. The mean survival time of the patients with nuclear staining with E2F1 and those without was 39% and 55%, respectively. The relationship between these results was statistically insignificant (p=0.081). Relationship between E2F1 cytoplasmic staining and survival rates was also investigated. The average overall survival rate of the cases with E2F1 cytoplasmic staining was 48% and that of cases without E2F1 cytoplasmic staining was 56%. These differences were statistically insignificant (p=0.408) (Table 3).

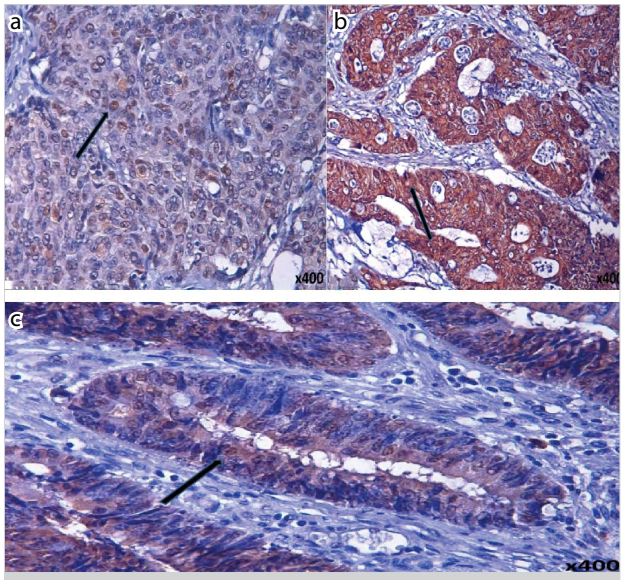

Figure 1. a-c. Immunohistochemical staining of E2F1. Magnification, x400. Nuclear (a), cytoplasmic (b), both nuclear and cytoplasmic staining of E2F1 (c)

Survival was investigated according to the degree of nuclear staining: strong and weak nuclear staining. When two groups were compared according to their degree of staining, there was a significant difference between the group with strong nuclear staining and that with weak staining (Table 4)

When the patients were evaluated according to the stage and E2F1 nuclear staining, no significant difference was found between them (p=0.212) (Table 5). Similarly when the cases were classified according to the degree of nuclear staining (as stained weakly or strongly) and were compared with stage, no significant difference was found between the groups (p=0.170). Patients were evaluated according to the stages in terms of E2F1 cytoplasmic staining and no statistically significant difference was found between the two groups (p=0.802). When the patients were classified according to the degree of cytoplasmic staining (as weak, medium, and strong stained) and were compared with the stages, there were no statistically significant results (p=0.766).

Fourteen patients (17.1%) received adjuvant chemoradiotherapy. There was no significant survival difference according to the nuclear staining degree in patients who received adjuvant chemoradiotherapy (p=0.22).

The relationship of age, tumor size, nuclear and cytoplasmic staining with survival was evaluated by Cox regression analysis. There was no statistically significant difference between tumor diameter and cytoplasmic staining, but there was a statistically significant difference between age and severity of nuclear staining (p=0.022). When the patients were evaluated according to the severity of nuclear staining, patients with a strong degree of nuclear staining had a 2.317-fold increase in the likelihood of survival compared with patients with a weak degree of nuclear staining.

DISCUSSION

One of the necessary steps in the treatment of the cancer is the development of molecular markers that help predict survival, potential behavior, and aggressiveness of the tumor. In

Table 3. Survival rates according to nuclear and cytoplasmic staining

Staining	12-month survival rate (%)	24-month survival rate (%)	36-month survival rate (%)	48-month survival rate (%)	60-month survival rate (%)	Mean (%)	p
Nuclear stained	76	46	38	33	29	39	0.081
Nuclear unstained	79	69	59	55	48	55	
Cytoplasmic staining	79	60	50	47	38	48	0.408

Table 4. Survival rates according to the degree of nuclear staining

Degree of nuclear staining	12-Month survival rate (%)	24-Month survival rate (%)	36-Month survival rate (%)	Mean (%)	p
Strong nuclear staining	86	71	57	60	0.017
Weak nuclear staining	65	35	24	28	

Table 5. Analysis of patients according to the stage and E2F1 nuclear staining

		Nuclear staining	
	Total n (%)	Stained n (%)	Unstained n (%)
Stage I	10 (12.2)	2 (20)	8 (80)
Stage II	34 (41.5)	7 (20.6)	27 (79.6)
Stage III	26 (31.7)	9 (34.6)	17 (65.4)
Stage IV	12 (14.6)	6 (50)	6 (50)
Total	82 (100)	24 (29)	58 (71)

the literature, several studies have been performed in recent years to address this deficiency (17-19). E2F1 is a transcription factor that has been studied in many tumor types, except for rectal tumors, for its prognostic value.

E2F transcription factor 1 has a role in the G1/S phase transition of the cell cycle. In the transition of G1/S, Rb-E2F complexes are separated and E2F1 starts activating the transcription of many genes required for mitosis. The cyclin-dependent kinase-cyclin complex causes the separation of the Rb-E2F complex with Rb phosphorylation (20-22). P16 is a tumor suppressor gene product that prevents the creation of a complex between cyclin and cyclin-dependent kinase (23). Dong et al. (24) showed that E2F1 induces apoptosis in both normal and malignant cells. They also demonstrated that E2F1-dependent apoptosis could be independent of p53. Gene transfer to adenovirus with E2F1 is also effective in antitumor activity, with lower doses of chemotherapeutic agents (25). In the study of Xie et al. (26), E2F1 (+) plasmids were transfected into cells and it was shown that apoptosis increases, cell growth slows, and the cell cycle stops at the G2/M phase in gastric cancer. It is thought that E2F1 has a function as a tumor suppressor. La Belle et al. (5) investigated the role of E2F1 in programmed cell death. However, it has not been clearly elucidated if it works as an oncogene or a tumor suppressor. Bramis et al. (4) suggested that E2F1 was a tumor suppressor in colon cancer. Lee et al. (9) reported that in gastric cancer patients, the reactivity of E2F1 can predict overall survival rates independently.

In our study, when patients are grouped as E2F1 nuclear stained or not, the average survival of the E2F1 stained group is 39% and that of the unstained group is 55%. These results were statistically insignificant (p=0.081). If patients were evaluated according to their degree of nuclear staining, the median overall survival of cases with strong nuclear staining was 60% and that for those with weak nuclear staining was 28%. There was a statistically significant difference between the groups according to their degree of nuclear staining (p=0.017). These findings showed that the degree of staining is more decisive according to the presence of staining, for more influence, more E2F1 nuclear staining activity is necessary. The answer to the question why there is a significant difference in survival between strong staining and unstained groups remained to be elucidated with larger studies. When E2F1 cytoplasmic staining was evaluated, the average survival rate of the cytoplasmic staining-positive group was 48% and the average survival rate of the unstained group was 56%. This difference was statistically insignificant (p=0.408). It is suggested that the main effect of E2F1 is on the core. When the correlations between the stages of the disease and nuclear or cytoplasmic stainings were evaluated, any significant difference was not obtained according to both the intensity of the staining and staining alone. Because there was no correlation between E2F1 staining of either nucleus or the cytoplasm and the stages, we may assume that E2F1 plays a role independently from the stage, which means that in some tumors, tumor progression is not dependent on E2F1, whereas in some tumors, E2F1 plays a role from the beginning of the process. Further studies are certainly warranted to address this issue.

Cox regression analysis was used to evaluate the association of age, tumor diameter and cytoplasmic staining with survival. No statistically significant difference was found between tumor diameter and cytoplasmic staining, but the difference between age and degree of nuclear staining was statistically significant (p=0.022). Patients with a strong degree of nuclear staining had a 2.3-fold increase in chances of survival compared with patients with weak staining (p=0.010). These findings suggest that E2F1 does not stimulate cellular proliferation and differentiation but increases apoptosis in rectal cancer as in colon and prostate cancer.

CONCLUSION

As a result, E2F1 is effective, depending on the cell type and signals, and can act as an oncogene or tumor suppressor. It is found to be a poor prognostic parameter in lung, breast, esophageal, and pancreatic cancer, but it also has a protective effect by increasing apoptosis in colon, bladder, and prostate cancer.

Despite the relatively small number of cases, as the first study in the literature, our study demonstrated that E2F1 is a molecular marker that may predict the behavior and aggression of rectal cancer.

Ethics Committee Approval Ethics committee approval was received for this study from the ethics committee of Erciyes University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.A.; Design - A.A.; Supervision - E.S.; Resource - B.Ö.; Materials - H.U.; Data Collection and/or Processing - H.U.; Analysis and/or Interpretation - H.U.; Literature Search - H.U.; Writing Manuscript - H.U.; Critical Reviews - H.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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Assessment of the relationship between neutrophil lymphocyte ratio and prognostic factors in non-metastatic colorectal cancer

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ABSTRACT

Objective: Neutrophil-lymphocyte ratio still has a limited clinical use due to many non-cancer factors affecting neutrophils or lymphocytes in the present time. We aimed to evaluate the association between preoperative neutrophil-lymphocyte ratio and poor prognostic factors after curative elective colorectal surgery.

Material and Methods: This clinical retrospective study was initiated with 95 patients, who had a curative surgical resection between 2003 and 2013. The patients were divided into two groups based on the preoperative neutrophil-lymphocyte ratio cut-off value above and below 3. The groups were compared for tumor localization, diameter, and staging; the histopathological perineural invasion; lymphovascular invasion; and overall survival. Univariate and multivariate Cox regression analyses were used to determine the role of neutrophil-lymphocyte ratio after stratification by several clinicopathological factors.

Results: The mean age of patients was 59.79±1.48 (range, 23-90) years, and median follow-up period was 20.77±14.85 months. There was no significant difference in perineural or lymphovascular invasion, tumor size, stage, age, sex, and tumor location between the groups [Group 1 ratio >3 (n=52) and Group 2 ratio ≤3(n=43)]. Hemoglobin (p=0.035) and albumin levels (p=0.004) were lower in the Group 1. When the stage increased, differences between the rectal cancer groups were found. Overall survival was significantly lower in the Group 1 (p=0.013).

Conclusions: The study showed that a high neutrophil-lymphocyte ratio had an adverse effect on overall survival in colorectal cancer patients who had a curative surgery. However, we could not establish any association between neutrophil-lymphocyte ratio and the factors such lymphovascular invasion, perineural invasion, tumor size expect hemoglobin and serum albumin levels.

Keywords: Colorectal cancer, lymphocyte, neutrophil, surgery, overall survival

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INTRODUCTION

Colorectal cancer is the third most common malignancy worldwide. The number of deaths from colorectal cancer is 15.9 per 100,000 individuals per year. Approximately 4.7% of men and women are diagnosed with colon and rectal cancer at some point during their lifetime (1). Estimated preoperative prognosis for colorectal cancer patients will help the choice and modality of the surgical and medical treatment.

An improved lifespan has been shown with an intensive lymphocytic infiltration in localized tumors in the colorectal cancer patients (2-4). Additionally, some parameters, such as C-reactive protein and hypoalbuminemia, which show a poor prognostic association between systemic inflammatory response and colorectal cancer have been discussed (5, 6). Systemic inflammation has been reported to be an independent determining factor for prognosis in colorectal patients after surgery (5). A high neutrophil-lymphocyte ratio (NLR) has been reported to estimate poor outcomes in colorectal cancer patients who are exposed to primary resection (7). Ding (8) reported that a high NLR may establish the risk groups and in such patients NLR may be a marker in response at adjuvant cancer therapy.

Considering the histopathology of colorectal diseases, it is known that lymphovascular and perineural invasion have an adverse effect on prognosis. The most important prognostic variable in colorectal carcinoma is the presence or absence of lymph node metastases. In a study of more than 1000 operative specimens, Morson and Dawson (9) found regional venous involvement in 35% of cases. Submucosal venous spread occurred in 10% of cases, and there was an evidence of permeation of extramural vessels in 25% cases. In the former cases, there was little or no effect on prognosis; however, extramural venous involvement reduced five-year survival rates from 55% to approximately 30%.

Perineural invasion (PNI) has been shown to have a detrimental effect on the prognosis (10). Its presence may be a part of overall penetration of the bowel wall. The relationship between PNI and the advanced colorectal cancer patients was reported in 1981 (11). Krasna et al. (12) found that the three-year survival rate decreased from 57.7% in patients without neural invasion to 29.6% in patients with neural invasion.

Of 128 operative specimens examined by Horn, Dahl, and Morild (13), neural invasion was demonstrated in 32%. The five-year survival rate in patients with neural invasion was 64.3% compared with 81.1% when neural invasion was not demonstrated. A grading system was established based on the "intensity" (number of the perineural invasion foci in a 20-power field) and "depth" (distance from the muscularis propria). The PNI grading system may be useful in prognosis, and may allow case selection for intensive postoperative adjuvant therapy.

The present study has aimed to evaluate the association between NLR levels and prognostic factors in colorectal cancer patients who have a curative elective surgical resection.

MATERIAL AND METHODS

The present study retrospectively evaluated the files and the electronic data of patients who were surgically treated with the diagnosis of a colorectal cancer between January 2003 and December 2013 in the Gaziantep University Hospital. The study was approved by the Gaziantep University Local Ethics Committee with the decision no: 20.01.2014/48.

The patients for whom file data could not be completely accessed, who could not be followed up, who did not have detailed pathological examinations, who underwent an urgent surgery (due to perforation or obstruction), who had preoperative infections, who had a history of hematological disease or chronic inflammatory diseases, who received preoperative chemotherapy, and who had distant metastases were excluded.

Based on these criteria, among 268 patients who underwent colorectal cancer surgery, we included 95 patients who were diagnosed with adenocarcinoma and had only a curative surgery.

Patients' age, gender, tumor localization, tumor diameter, tumor classification, staging, presence or absence of a histopathological perineural, and lymphovascular invasion were recorded. The evaluation of vascular invasion was based on whether there was extramural involvement. Any pathological grading system was not used for the determination of perineural invasion. The lifetime data of the patients were collected using the hospital and the national databases.

From laboratory tests studied within last one week before surgery, the levels of neutrophils, lymphocytes, hemoglobin, and albumin were recorded. NLR was calculated. The values with the highest sensitivity and specificity were analyzed for NLR cut-off value based on cut-off values established according to the ROC curve analyses in some previous studies with a large number of patients (14, 15). The patients were divided into two groups based on an NLR cut-off value of three. Clinical-pathological characteristics and overall survival (OS) were compared between two groups.

Statistical Analysis

Descriptive analyses were conducted for the demographic parameters. Clinical-pathological characteristics between the groups were analyzed using Mann-Whitney U test and chi-square test, which are non-parametric tests. The survival was analyzed using Kaplan-Meier survival analysis. Univariate and multivariate survival analyses were made for the association between NLR and clinical and pathological parameters in OS. The Statistical Package for the Social Sciences 22.0 for system (IBM Corp.; Armonk, NY, USA) was used as statistical program.

RESULTS

The clinical and the pathological characteristics of the 95 patients who had a curative resection with the diagnosis of the colorectal cancer were studied. The mean age was 59.79±1.48 (range: 23-90) years. The female/male ratio was 40/55 (57.9%/42.1%). The median follow-up duration was 20.77±14.85 months. The tumor localization was in the colon (54.74%) and in the rectum (45.26%). The most common localization in the colon cancer form was the sigmoid colon and the right colon (Table 1).

The groups were based on NLR>3 (n=52) and NLR≤3 (n=43). Table 2 compares the clinicopathological characteristics between the groups. There was no difference in the age and sex distribution between the groups. There was a difference between the groups according to the localization of the colon and rectum, but it was not statistically significant (p=0.060). The proportion of colon/rectum patients was 33/19 in Group 1 and 19/24 in Group 2. Therefore, the colon and rectum cases were evaluated separately according to the stage. There were differences in stage 2 colon cancer between the colon groups. However, this situation did not reflect in stage 3 colon cancer. There were differences between the groups with regard to the stage 2 and 3 rectal cancer. This situation suggested that a high NLR is important in intermediate stage rectal cancer.

No significant difference was noted between NLR level and perineural or lymphovascular invasion. Lower hemoglobin and albumin levels in the high-NLR group were the only differences.

Table 1. Clinical and pathological features of patients

	Number of patients (percent)
Sex ratio (Female:Male)	40:55 (47%-53%)
Age (years)	59.79±1.48 (23-90)
Site of colorectal cancer	n (%)
Right colon	16 (16.84)
Transvers colon	5 (5.26)
Left colon	6 (6.31)
Sigmoid colon	25 (26.31)
Rectum	43 (45.26)
Stage	n (%)
Stage 1	15 (15.78)
Stage 2	35 (36.84)
Stage 3	45 (47.36)
Tumor size (cm)	5.13±2.04 (1.20-13.00)
Follow up (month) [mean, SD, (min-max)]	20.77±14.85 (1-82)
Hemoglobin	12.19±1.94 (6.7-16.30)
Albumin	3.86±0.55 (2.16-4.90)

Table 2. The features of patients with high and low NLRs

		NLR>3 (n:52)	NLR≤3 (n:43)	p
Age		62.13±14.81 (23-90)	56.95±13.66 (28-79)	0.063
Sex (Female/Male)		18/34	22/21	0.156
Locations	Colon	33 (63.46%)	19 (44.19%)	0.130
	Rectum	19 (36.54%)	24 (55.81%)	
Tumor size		5.13±2.12 (2-11)	5.10±1.95 (1.2-13)	0.795
Colon Stage	1	4/33	1/19	0.200
	2	14/33	9/19	0.033*
	3	15/33	9/19	0.087
Rectum Stage	1	2/19	8/24	0.164
	2	5/19	7/24	0.002*
	3	12/19	9/24	0.003*
T	1	3 85.76%)	2 (4.65%)	0.636
	2	7 (13.46%)	9 (20.93%)	
	3	32 (61.53%)	27 (62.79%)	
	4	10 (19.23%)	5 (11.62%)	
N	0	25 (4.07%)	25 (58.13%)	0.616
	1	14 (26.92%)	9 (20.93%)	
	2	13 (25.00%)	9 (20.93%)	
Perineural invasion	Negative	36 (69.23%)	32 (74.41%)	0.742
	Positive	16 (30.76%)	11 (25.58%)	
Lymphovascular invasion	Negative	32 (61.53%)	25 (58.13%)	0.899
	Positive	20 (38.46%)	18 (41.86%)	
Hemoglobin		11.84±1.82 (8.4-15.6)	12.63±2.03 (6.7-16.3)	0.035*
Albumin		3.70±0.58 (2.16-4.67)	4.04±0.48 (2.8-4.9)	0.004*

NLR: neutrophil-lymphocyte ratio; T: tumour size staging; N: lymph node metastasis staging
*p<0.05

For all patients, the two-year and the five-year OS were 75.6% and 66.0%, respectively. As of August 2014, 18 and six patients died in high-NLR and low-NLR groups, respectively. Figure 1 presents the OS graph of the groups. High NLR was related with significantly poor OS outcomes (Log-rank test, p=0.013).

To investigate whether NLR was associated with clinical and pathological outcomes, univariate and multivariate survival analyses for OS was performed.

Univariate analysis revealed high NLR as a poor prognostic indicator of OS outcomes of patients, whereas age, gender, pathological T and N stages, tumor size, lymphovascular invasion, and perineural invasion were not significantly associated with OS.

A similar result was noted with multivariate analysis as well. High NLR was identified as an independent prognostic factor for OS [hazards ratio (HR)=3.003; 95% CI=1.189-7.589; p=0.02] as outlined in Table 3.

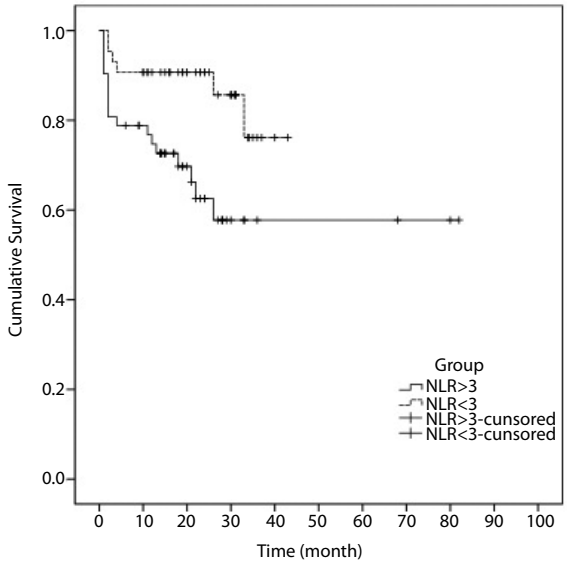

Figure 1. Kaplan-Meier curves for OS of the patients with colorectal cancer based on the NLR groups

DISCUSSION

Colorectal cancers have an important role in deaths from cancer worldwide. Local recurrence and distant metastases may occur in the advanced periods even in patients who have undergone curative resection. High preoperative NLR is associated with poor prognostic factors in colorectal cancer (16).

The study by Roxburgh suggested that low peritumoral infiltration and increased systemic inflammation were linked via the cell-mediated immune system. Both the pathologic and the biochemical measures of the inflammatory response predicted the survival after colorectal cancer surgery (17). In a study of 374 patients (229 with negative node disease) who underwent a surgery between 1986 and 1996, the systemic inflammatory response measured by Glasgow prognostic score (mGPS) criteria was neither associated with Dukes stage nor with peritumoral infiltration, but was associated with an increased number of circulating total white blood cells and neutrophils and a decreased number of circulating lymphocytes. mGPS was also independently associated with cancer-specific survival in patients potentially undergoing a curative resection for colorectal cancer (18).

This present study evaluated several clinical and pathological characteristics including perineural and lymphovascular invasion, but could not establish a significant correlation between NLR and such parameters. Only hemoglobin and albumin levels were significantly lower in the high NLR group.

This study showed that high NLR significantly affected OS. However, no significant correlation was established between NLR and perineural and lymphovascular invasion, which are known to be poor prognostic factors. It may also be affected by the exclusion of the stage 4 patients, receiving neoadjuvant chemoradiotherapy based on evaluation of the association between NLR and perineural-lymphovascular invasion. This is

Table 3. Univariate and multivariate analyses of clinicopathological parameters for the prediction of OS in the patients with colorectal cancer

		Univariate analysis		Multivariate analysis	
		HR (95.0%CI)	p	HR (95.0%CI)	p
Age		1.028 (0.995-1.062)	0.099	1.030 (0.993-1.069)	0.118
Sex	(male vs female)	1.867 (0.774-4.506)	0.165	1.376 (0.488-3.883)	0.547
Tumor size		1.149 (0.965-1.367)	0.119	1.198 (0.970-1.480)	0.093
T	T1	1	0.351	1	
	T2 (2 vs 1)	0.289 (0.018-4.646)	0.381	0.197 (0.011-3.597)	0.273
	T3 (3 vs 1)	1.737 (0.231-13.058)	0.592	0.772 (0.082-7.284)	0.821
	T4 (4 vs 1)	1.727 (0.192-15.551)	0.626	0.663 (0.061-7.243)	0.736
N	N0	1	0.246	1	
	N1 (1 vs 0)	1.614 (0.600-4.339)	0.343	0.994 (0.192-5.136)	0.994
	N2 (2 vs 0)	2.242 (0.864-5.817)	0.097	1.301 (0.189-8.977)	0.789
PN invasion	Positive vs negative	1.771 (0.786-3.988)	0.168	1.376 (0.483-3.920)	0.550
LV invasion	Positive vs negative	2.133 (0.947-4.805)	0.068	1.747 (0.306-9.982)	0.531
Hemoglobin		1.007 (0.819-1.237)	0.947	1.042 (0.792-1.371)	0.770
Albumin		0.630 (0.322-1.231)	0.177	0.958 (0.390-2.352)	0.926
Groups	(NLR>3 vs NLR≤3)	3.003 (1.189-7.589)	0.020*	3.055 (1.080-8.638)	0.035*

OS: overall survival; PN: perineural invasion; LV: lymphovascular; T: tumour size staging; N: lymph node metastasis staging; HR: hazard ratio; CI: confidence interval
*p<0.05

due to the fact that such invasions are more frequent in advanced stage patients.

Ozdemir et al. (19) in their study, found by the univariate analysis that there is a correlation between high NLR and pathologic nodal stage of bad OS. However, in our study, there was no statistical correlation established by univariate and multivariate analysis between groups in terms of lymphovascular invasion and TNM stage. A reason of this difference may be the exclusion of study of metastatic patients.

Intratumoral immun T cell densities on the colon or the rectum are especially associated with tumor enlargement and metastasis (20). There is a significant difference in the advanced rectum cancer groups. As in many studies, we did not divided the colon and rectal tumor patients in this study. Moreover, there was no significant difference in tumor localizations. However, increasing the number of cases due to the distinction between the colon and the rectal tumors may have different consequences.

Although NLR test has advantages such as being simple and affordable and the ability to study among routine tests, it may be affected by several external factors. Non-randomization and the reduced number of patients were disadvantages of this study.

If the study's design had been prospective, the standardization of preoperative whole blood count and evaluation of specimens by the same pathologists might have affected the results.

Neutrophil-lymphocyte ratio may have a sufficient prognostic value alone when evaluated together with the literature. However, it still has limited clinical use due to many non-carcinogenic and carcinogenic factors affecting neutrophil and lymphocyte counts in daily use.

We think that this matter will be clarified with more detailed meta-analyses in large-scale studies.

CONCLUSION

The study showed that high NLR has an adverse effect on the OS in patients who have undergone a curative surgery. However, we could not establish any association between NLR and the factors such lymphovascular invasion, perineural invasion, and tumor size, except hemoglobin and serum albumin levels.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (20.01.2014/48).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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The Whitehead operation procedure: Is it a useful technique?

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ABSTRACT

Objective: Hemorrhoidal disease is a very common entity in the general population; however, the therapeutic approaches to hemorrhoids remain controversial. The choice of treatment method depends on the grade of the hemorrhoid as well as the experience of the surgeon. The Whitehead hemorrhoidectomy procedure is often applied for grade IV hemorrhoids.

Material and Methods: We studied 49 patients who underwent surgery between December 1982 and January 2013. The indications for the Whitehead procedure in all patients were grade IV hemorrhoidal disease. The data on these patients were evaluated retrospectively with respect to age, gender, preoperative diagnosis, and postoperative complications.

Results: Of the patients included in this study, 34 were male and 15 were female. The mean age of the patients was 41.93±12.42, and the age range was 24-70 years. Complications of the Whitehead procedure included bleeding (6.12%, three cases), stricture (2.04%, one case), urinary retention (16.33%, eight cases), and temporary anal incontinence (2.04%, one case). No patients developed Whitehead deformities, entropion, or infectious complications. All patients were discharged from hospital between the fifth and eighth days post-surgery (6.45±1.00 days). The follow-up period was 1-234 months (70.02±54.89).

Conclusion: The Whitehead procedure is successful in patients with prevalent peripheral prolapse and/or thrombosed hemorrhoids. With the right indications, and if the surgeon has adequate experience, the morbidity rate of the Whitehead procedure is similar to that of other treatment methods.

Keywords: Whitehead, hemorrhoidectomy, hemorrhoidal disease, complication

INTRODUCTION

Hemorrhoidal disease has been a well-known entity in general surgery for many centuries, with bleeding, anal pain, and distress being the most common symptoms. The therapeutic approaches to hemorrhoids remain controversial; the choice of treatment method depends on the grade of the hemorrhoid as well as the experience of the surgeon.

Hemorrhoidectomies are the oldest and most common surgical techniques used for the treatment of hemorrhoids. In this report, 49 cases of patients with grade IV hemorrhoidal disease who were treated using the Whitehead procedure are presented.

MATERIAL AND METHODS

Forty-nine patients who underwent the Whitehead procedure between December 1982 and January 2013 were evaluated retrospectively. Age, gender, preoperative diagnosis, postoperative complications, and length of hospital stay were evaluated. The indication for surgical treatment was grade IV hemorrhoidal disease in all the patients. Table 1 shows our algorithm for the treatment of hemorrhoidal disease.

Informed consent was not received due to the retrospective nature of the study. This research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".

Preoperative Preparation

All patients received mechanical colonic preparation. This began 24 h before the surgery. Additionally, a fiber diet was applied during this period. In patients who were admitted with acute hemorrhoidal attacks (thrombosed, irreducible, or inflamed hemorrhoids), medical treatment methods, including corticosteroids, laxative agents, and warm antiseptic sitting baths, were applied prior to surgery. Surgical treatment was also delayed until the acute symptoms and signs resolved.

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Surgical Procedure

Under general or spinal anesthesia, anal dilatation was performed using two fingers with the patient in the gynecological position. An incision was then made in the skin-mucosal line extending from the 12 o'clock point to the 6 o'clock point. The anal mucosa was dissected, together with the hemorrhoidal packages, up to the dentate line (Figure 1). Following this, another incision was made from the skin to the superior part of the dentate line, and the skin was sutured to the rectal mucosa. Later, the left half of the anal mucosa was excised from just above the dentate line, and the mucosa was sutured to the skin. The same procedure was applied symmetrically to the remaining reciprocal part of the anal mucosa (Figure 2). After hemostasis, a rectal tube surrounded by Spongostan was inserted through the anal canal (Figure 3).

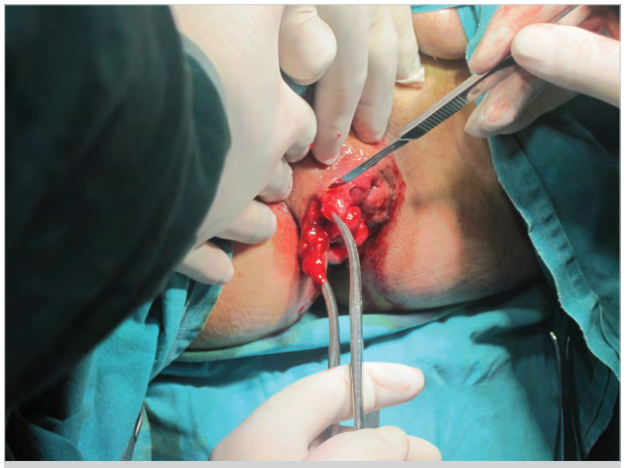

Figure 1. The anal mucosa was dissected together with the hemorrhoidal packages until the dentate line

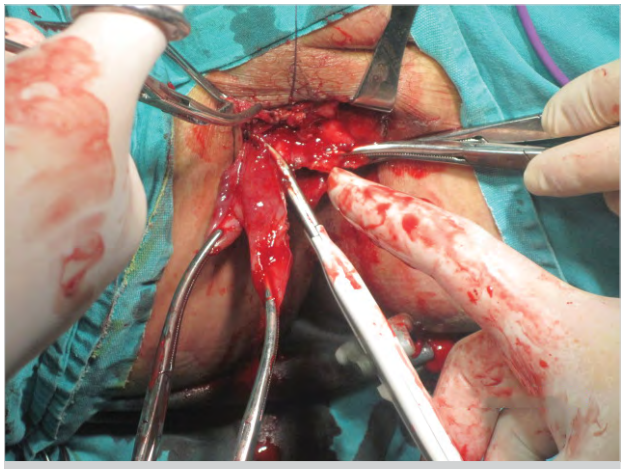

Figure 2. The same procedure was applied symmetrically to the reciprocal remaining part of the anal mucosa

Postoperative Follow-Up

All patients received parenteral spasmolytic and analgesic therapy for three postoperative days; if necessary, oral therapy was continued after this time. The rectal tube was maintained in place for three days in 48 patients. Intestinal peristalsis returned to normal during this period; however, in one patient, the rectal tube was removed on the first day because of intolerance.

All patients were maintained on a liquid diet for the first and second postoperative days. A normal diet was resumed on the third postoperative day.

After removal of the rectal tube, the patients received a warm antiseptic sitting bath following defecation. The anastomotic suture line was evaluated by rectal digital examination on the tenth and the thirteenth postoperative days.

RESULTS

Of the 49 patients who were included in this study, 34 were male and 15 were female. The mean age of the patients was 41.93±12.42, and the age range was 24-70 years.

The indications for surgical treatment were grade IV hemorrhoidal disease in all patients, anal fissures in three of the patients, and an iatrogenic sigmoid colon laceration related to rectoscopy (at another clinic) in one patient. In the last patient, the colon was repaired concurrently with the Whitehead procedure.

Twenty-three patients (46.94%) with extensive acute thromboses and inflammation received medical treatment, including diet, laxatives, and local analgesics, as well as cortisone

Table 1. Classification, grading, and treatment of hemorrhoidal disease

Classification	Grade	Findings	Treatment
Internal	Ia	Hemorrhoids protrude into but do not prolapse out of the anal canal	M, AD, RBL, IP, SCL, CRY, EC
	Ib	Thrombosis of Grade Ia hemorrhoids	M and/or H
	II	Hemorrhoids prolapse out of the anal canal with bowel movements or straining, but spontaneously reduce	M, PHSP, RBL, IP, SCL, CRY, EC
	III	Hemorrhoids prolapse during the previously described maneuvers and must be manually reduced by the patient	M, RBL, IP, SCL, CRY, EC, H, PPH
	IVa	Hemorrhoids are prolapsed out of the anus and cannot be reduced	Whitehead procedure, two-step hemorrhoidectomy
	IVb	Extensive acute thrombosis and inflammation of Grade IVa hemorrhoids	M
External		Even if complicated	M, AD, excisional H

M: medical treatment including diet, stool-bulking agents, analgesia, and local applications; AD: anal dilatation; RBL: rubber band ligation; IP: infrared photocoagulation; SCL: sclerotherapy; CRY: cryotherapy; EC: electrocautery; H: hemorrhoidectomy (open, closed, stapled); PHSP: procedures for high sphincteric pressure; PPH: procedure for prolapsing hemorrhoids

Figure 3. A rectal tube was placed

Table 2. Patient complications

Complication	n	%
Bleeding requiring no intervention	3	6.12
Stricture	1	2.04
Urinary retention	8	16.33
Temporary anal incontinence	1	2.04
Total	13	26.53

applications for three to seven days. These patients underwent operations after the acute stage. Three patients (6.12%) developed bleeding that did not require invasive therapy or transfusions during the early postoperative period (first 24 h). In the second month postoperatively, a stricture developed in one patient (2.04%) in whom the rectal tube was removed early due to intolerance and on whom postoperative follow-up could not be performed. This patient was treated by repeated anal dilation.

Eight patients (16.33%) had urinary retention, and a urinary catheter was inserted for 24-48 h. One patient had anal incontinence for two days following the removal of the rectal tube, which recovered spontaneously. The total morbidity rate was 26.53% (Table 2).

No patients developed Whitehead deformities, entropion, or infectious complications (Table 2), and all patients were discharged from the hospital between the fifth and eighth days (6.45±1.00 days). The follow-up period ranged from 1 to 234 months (70.02±54.89).

DISCUSSION

Hemorrhoids are mainly divided into two types: external and internal. They are also described on the basis of size and clinical findings; additionally, internal hemorrhoids are subdivided into four grades (1, 2).

This grading of internal hemorrhoids can be confused by complicated cases. For example, the approach to a grade I thrombosed hemorrhoid is different from the approach to a non-thrombosed hemorrhoid. Most cases of grade IV hemorrhoids involve extensive acute thromboses and inflammation; these cases can be transformed to grade III by medical treatment. Thus, we added two subgroups, grades Ib and IVb. Grades I and IV in the classical grading system were referred to as grades Ia and IVa. Cases with thromboses and extensive acute thromboses and inflammation were described as grades Ib and IVb, respectively (Table 1).

Diet and stool-bulking agents, rubber band ligation, infrared photocoagulation, sclerotherapy, cryotherapy, and electrocautery can be used for cases of grade I to III hemorrhoids. Surgical methods such as open or closed hemorrhoidectomy, stapled hemorrhoidectomy, and the procedure for prolapsing hemorrhoids (PPH) are procedures used for the treatment of grade III and IV cases.

Since 1882, the Whitehead procedure has been widely applied for grade IV hemorrhoids; although stapled hemorrhoidectomy and PPH have commonly been used in recent decades, they have not been found to be as successful due to high morbidity and recurrence rates (2-4). Although the Whitehead hemorrhoidectomy is controversial, it is used for grade IV hemorrhoids; furthermore, despite the common occurrence of prolapsed and/or thrombosed hemorrhoids and partial resection, it has absolute indications (5, 6).

The circumferential excision of the anal mucosa and hemorrhoids was first reported by Walter Whitehead (7) in 1882; however, this procedure is less preferred due to technical difficulties and a high morbidity rate. Malpractice suits also have a strong effect on these results.

During the last quarter of the 20th century, the Whitehead procedure attracted attention. White et al. (8), Barrios et al. (9), Sagar and Wolff (10), Burchell (11), Bonello (12), and others (13-22) have reported large and successful studies with modifications of Whitehead's technique.

Complications from the Whitehead procedure are stenosis (up to 8.8%), ectropion or wet anus (Whitehead's deformity), anal incontinence (2%-12%), severe pain (up to 50%), urinary retention (2%-50%), fecal impaction (0.3%), intraoperative blood loss or postoperative bleeding (0.03%-6%), fistula or abscess (1.1%), complications of wound healing (1%-2%), and infection (0.5%-5.5%) (5, 13, 14, 20-22).

Stricture arises from fibrotic tissue proliferating and obstructing the fecal passage during the wound healing process. Although it was more frequent in the past, its incidence has been reported as less than 10% in recent publications. Stricture is prevented by regular defecation; however, the frequency of the disease increases in patients avoiding defecation due to high sphincter pressure and excessive pain. Sphincter spasm is a factor that can increase ischemia at the anastomosis; older patients have a higher risk for developing stenosis after Whitehead surgery due to sphincter spasm (15). Anal dilation is usually adequate for prevention and treatment; additionally, posterior or lateral sphincterotomy can be beneficial (16-19).

In the early stages of stricture formation, anal dilation is usually a sufficient treatment; however, in delayed cases, anoplasty may be beneficial (23). In our study, a rectal tube was maintained in the anal canal for three days for the prevention of stenosis; except for a slight increase in pain, no side effects were observed. Conversely, one patient who did not tolerate the rectal tube developed stenosis following its removal.

The Whitehead deformity occurs as a result of rotation of the mucosa into the anal canal or outward skin due to malformation of the mucosal line. It may result from a technical error or dehiscence of the suture line. Another cause may be interventions made during a period of extensive acute thrombosis and inflammation. Technical errors may occur due to the undetermined skin-mucosal line during that period. There are two basic ways to prevent Whitehead deformity: performing a skin-to-mucosal line incision at the borderline and delaying surgery by applying medical treatment in cases of acute thrombosis and inflammation. All Grade IVb patients received medical treatment and did not undergo surgery during the acute phase.

In cases of entropion, medical treatment (moisturizing-cortisone ointments) are useful. In cases of ectropion (wet anus), surgery is required. None of our patients developed the Whitehead deformity, entropion, or infectious complications.

Anal incontinence is caused by a decrease or loss of pressure in the anal sphincter. In most people with hemorrhoidal disease, the anal canal resting pressure is high. The internal sphincter accounts for 80% of the resting pressure in these cases. To decrease this pressure, a partial internal sphincterotomy or anal dilation is performed (24, 25). In our study, we observed that dilation performed under analgesia in grade I and grade II patients had a 95% success rate. In the patients who underwent the Whitehead procedure, anal dilation was performed routinely. We encountered short-term anal incontinence in only one patient.

Pain is associated with the incision in the anoderm and intervention in the sphincter (sphincterotomy or dilation). Spasmolytic analgesics, or even narcotic analgesics, may be necessary for treatment. These high levels of pain and weakness during bladder contractions are caused by disorders and innervation of the perianal region and may lead to urinary retention. We encountered urinary retention in eight patients; they were treated with urinary catheters for 24-48 h.

Fecal impaction can be seen in patients with inadequate preoperative bowel preparation. Another causative factor is avoidance of defecation by patients due to pain. Complete preoperative bowel preparation and administration of laxatives that increase bowel peristalsis are sufficient for prevention.

Intraoperative blood loss or postoperative bleeding can be caused by a lack of technical ability or by errors. In rare cases, rigorous application may require additional intervention. In this study, three patients (6.12%) developed bleeding that did not require invasive therapy or transfusions in the early postoperative period (first 24 h).

Fistula/abscess formation, infection, and wound disintegration result from inadequate preparations, chemoprevention, or techniques that are not method-specific.

The limitations of this study are the low number of patients and the lack of comparison with groups of patients who underwent other surgical procedures.

CONCLUSION

The Whitehead procedure provides successful results in patients with prevalent peripheral prolapse and/or thrombosed hemorrhoids. If the surgeon is experienced and the indications are correct, the morbidity rate is similar to that of other methods.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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Colonoscopic perforations: Single center experience and review of the literature

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ABSTRACT

Objective: Iatrogenic colonic perforation is a well-known complication that can increase mortality and morbidity in patients undergoing colonoscopy. Closer follow-up and a well-planned treatment strategy are required when perforation arises as a complication. The aims of this study are to (1) report our experience with a large colonoscopy series; (2) evaluate the underlying mechanisms of iatrogenic colonic perforation; (3) discuss the ideal period between onset and treatment; and (4) review the current literature regarding the management of iatrogenic colonic perforations.

Material and Methods: Patients who underwent colonoscopy between January 2005 and May 2015 at a single center were reviewed retrospectively. Procedures during which colonic perforations occurred were documented and analyzed.

Results: Between January 2005 and May 2015, 31,655 patients underwent colonoscopy and 5,214 patients underwent recto-sigmoidoscopy at our center. Thirteen of these procedures were associated with perforation. The perforation rate was found to be 0.041%. The most frequent locations of perforation were (a) the rectosigmoid junction, (b) the proximal rectum, and (c) the sigmoid colon. Management included surgical treatment in 11 patients and conservative management in 2 patients. Twelve patients (92.31%) were discharged uneventfully, and death occurred in one (7.69%) patient.

Conclusion: Although they are rarely encountered, colonic perforations are serious complications of colonoscopy. A high index of clinical suspicion is required for early diagnosis and appropriate treatment. Age, co-morbidities, the location and size of the perforation, and the time interval between onset and diagnosis should be evaluated, and the treatment approach should be planned accordingly.

Keywords: Colon perforation, colonoscopy, iatrogenic bowel perforation

INTRODUCTION

Colonoscopy is accepted as the gold standard imaging modality for the diagnosis of colon and distal ileum diseases. It aids the detection of smaller lesions and tissue sampling and also functions as a therapeutic procedure for intestinal diseases. Similar to other invasive procedures, colonoscopy has been associated with various complications; among these, perforation is the most important. Iatrogenic colonic perforation has high rates of mortality and morbidity. It is mainly divided into two categories: diagnostic and therapeutic (1, 2). Management includes both medical and surgical approaches. However, the best approach for treatment depends on various factors, such as the patient's general condition, age, co-morbidities, and, most importantly, the time between the onset and diagnosis of perforation. In this study, we aimed to evaluate the incidence of perforation in a large colonoscopy series, discuss patient management strategies, and analyze the clinical consequences of iatrogenic colonic perforation.

MATERIAL AND METHODS

Between January 2005 and May 2015, a total of 31,655 lower GIS endoscopies were performed at our center. Patients with iatrogenic colonic perforations were investigated retrospectively. All procedures were conducted under sedoanalgesia. The procedures were performed by 27 endoscopists, including 24 general surgeons and 3 gastroenterology specialists. The experience of the endoscopists varied between 2 and 15 years.

We analyzed the demographic characteristics of the patients, the type of procedure (therapeutic or diagnostic), indications for colonoscopy and associated colonic disease, location and detection time of perforation, management strategy (operative or nonoperative), and complications.

The perforations were detected either during colonoscopy by observing a visible defect in the colonic wall (mesenteric or antimesenteric side) or after the procedure by detecting free intra-abdominal air upon radiological examination. Patients who complained of abdominal pain or distention following

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colonoscopy were initially evaluated by abdominal x-ray. All patients with generalized peritonitis and free intra-abdominal air underwent surgical intervention.

Ethics committee approval was not required due to the retrospective nature of the study. All data were collected from the accessible computer database system of the hospital. Written informed consent was obtained from all patients included in this study. The information was collected in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM Corp.; Armonk, NY, USA) 22.0 software package.

Table 1. Distribution of procedures by year

Year	Colonoscopies	RSS	Perforations (n)
2005	594	170	-
2006	1620	410	-
2007	2241	595	2
2008	3024	950	1
2009	4050	800	1
2010	5184	500	-
2011	4428	650	2
2012	5004	550	1
2013	4527	562	4
2014–2015 January to May	983	27	2
Total	31655	5214	13

RSS: rectosigmoidoscopy

RESULTS

Lower GIS endoscopies included 5,214 recto-sigmoidoscopy (RRS) and 31,655 colonoscopy procedures (Table 1). Perforation occurred in 13 (0.041%) patients. Perforated patients included five men and eight women. Their mean age was 63.8 (range 44 to 77) years. Indications for colonoscopies were as follows: sub-ileus (n=1266) (4%), constipation and abdominal pain (n=949) (3%), and investigation of the etiology of anemia (n=1900) (6%). Anatomic distribution of the perforations included the (i) proximal rectum (n=3), (ii) rectosigmoid junction (n=6), (iii) sigmoid colon (n=3), and (iv) ascending colon (n=1). Overall, iatrogenic perforations were recorded by 13 endoscopists who had variable years of endoscopic experience. Eight of the endoscopists had a mean experience of three (range two to five) years. Endoscopic experience varied from 5 to 10 years for three endoscopists and 10 to 15 years for two endoscopists. The times of diagnosis and the treatment approaches for each anatomic location of perforation are shown in Table 2. Perforation occurred during the procedure in nine patients. Seven of the patients whose colonic wall integrity was disrupted had abdominal pain, defense, or guarding as clinical symptoms. The other two patients did not show clinical symptoms of abdominal pain, guarding, or defense; in these patients, the site of perforation was found to be on the mesenteric side. In all patients who experienced perforation during the procedure, the management of choice was surgical. In all patients, primary colon repair was performed. In addition to primary colon repair, colostomy was performed in two patients and ileostomy in one patient.

Perforation was detected in four patients after colonoscopy. One patient was admitted to the emergency clinic due to acute abdominal pain following colonoscopy. Abdominal X-ray of the patient revealed free air under the diaphragm; the patient underwent an operation about six hours after the colonoscopy procedure. Perforation was observed in the rectosigmoid junction and treated with primary repair. Subcutaneous emphysema was observed in the neck of one patient

Table 2. Demographics, localization, time of diagnosis, and treatment of patients with perforation

Age	Gender	Localization (year)	Time of diagnosis	Treatment
76	M	Rectosigmoid junction (2007)	Perioperative	Primary repair
45	M	Ascending colon (2007)	12 hours later	Medical therapy
68	M	Rectosigmoid junction (2008)	Perioperative	Primary repair
71	F	Sigmoid colon (2009)	Perioperative	Primary repair
51	F	Sigmoid colon (2011)	Perioperative	Primary repair and ileostomy
69	M	Rectum (2011)	Perioperative	Primary repair
44	F	Rectosigmoid junction (2012)	6 hours later	Primary repair
68	F	Rectum (2013)	Perioperative	Primary repair and colostomy
77	F	Rectosigmoid junction (2013)	Perioperative	Primary repair
76	M	Rectosigmoid junction (2013)	8 hours later	Primary repair and colostomy
56	F	Rectosigmoid junction (2013)	Perioperative	Primary repair and colostomy
69	F	Rectum (2014)	Perioperative	Primary repair
60	F	Sigmoid colon (2015)	24 hours later	Exitus (refusal of surgery)

M: male; F: female

eight hours after the colonoscopy procedure. On exploration, perforation was detected in the proximal rectum. Primary repair with loop colostomy was performed due to peritonitis symptoms and accompanying comorbidity. One iatrogenic colon perforation occurred as a result of polypectomy. The patient had a history of repetitive polypectomy; further polypectomy was performed for polyps larger than 1 cm. He had fever and abdominal pain 12 hours after the colonoscopy procedure and was admitted to the emergency department. Subdiphragmatic free air was detected under the diaphragm in an abdominal X-ray. Secondary colon perforation was considered for the patient as a result of polypectomy. There were no peritonitis symptoms. The patient was discharged without complications with broad spectrum antibiotherapy. The other patient was admitted to hospital due to abdominal pain and symptoms of anemia; perforation was diagnosed 24 hours after the colonoscopy procedure. Due to rejection of surgery by the patient, it was decided to follow up the patient with medical treatment. Unfortunately, the patient died due to onset of sepsis 92 hours after the procedure.

The mortality rate was found to be 7.69% (1 in 13 patients). The average length of hospital stay was 15 (range: 5 to 48) days.

DISCUSSION

Colonoscopy is the gold standard for the diagnosis and follow-up of colonic diseases (3). Despite its superiority in diagnostic and therapeutic use, it can lead to serious complications. Previous reports have documented a wide array of complications, including electrolyte imbalances that occur during preparation for colonoscopy and sedation during the procedure. Therefore, patient monitoring during the procedure is important to reduce and prevent these complications (4). Other complications are iatrogenic in nature; these include hemorrhage and perforations. Perforation rates are reported to range between 0.02% and 0.8% for diagnostic colonoscopy and between 0.15% and 0.3% for therapeutic colonoscopy (1, 2). Regarding technique, endoscopic sub-mucosal dissection (ESD) is known to carry a higher perforation risk than endoscopic mucosal resection (EMR) or polypectomy (5, 6). The rate of hemorrhage has been reported to be 1% to 2% and is more visible after polypectomy and dilatation of structures compared to other procedures (7-9). Perforation may occur from direct mechanic effects (sharp edge) of the colonoscope, barotrauma, or thermal burns during polypectomy (5). While perforation resulting from direct mechanic effects is often seen in the recto-sigmoid junction and strictures, perforation resulting from direct barotrauma is most frequently seen in the cecum zone (1, 6).

Perforations that occur during therapeutic processes such as polypectomy are seen during polypectomies of polyps greater than 2 cm in size, similarly to our right colon case. Compared to flexible rectosigmoidoscopy, perforation rates during colonoscopies are two or four times higher (8, 9). In our study, no perforations occurred during rectosigmoidoscopy, thus obviating the need for a comparison of both approaches. Perforations are known to occur commonly at the recto-sigmoid junction. Reported reasons include angulation and transition challenges at the recto-sigmoid junction and thinning of the colonic wall at the ascending colon (10-12). In our series, the rate of perforation was seen most frequently (46%) in the recto-sigmoid junction.

Of the three (mechanical, barotraumas, and thermal) previously described mechanisms associated with colonoscopic perforations, mechanical is known to be the most common (13-15). It occurs after forcing the tip of the apparatus without direct visualization, making loops in the far areas, or penetrating a diverticulum (16, 17). Barotrauma is another important mechanism; it results from excessive gas insufflation leading to linear tear or full-thickness perforation of the serosa. Perforations due to barotrauma may occur in the right colon due to its width (18, 19). They can occur not only in the cecum but also in high-pressure zones such as angulations in the sigmoid colon or herniated loops that enter into the inguinal and ventral sacs (20).

For perforations related to colonoscopy, structural colonic pathologies (diverticular disease, inflammatory bowel diseases, megacolon) and patient-related factors (age, female gender, accompanying illnesses, previous abdominopelvic surgeries) have been reported as prognostic factors. Previous studies have shown that patients over 65 years of age present significant risks for perforation (1, 21-23). In some studies, it has been reported that the perforation rate in patients over 75 years of age can increase by four to six times compared to that in young patients (24, 25). Korman et al. (1), Anderson et al. (6), and Handami et al. (21) stated that female gender carries a higher risk for perforation, while Arora et al. (23) documented no correlation with gender. In our study, eight patients (61.5%) were female. Perforations in four patients were due to inadequate bowel preparation (sub-ileus state), and the other four patients had histories of gynecological surgery.

Handami et al. (21), Arora et al. (23) and Gatto et al. (24) observed that the perforation rate is higher in patients with two or more comorbidities. In our study, increased risk of colonic perforation was observed in patients with ASA scores greater than 3. Handami et al. (21) reported older age, female gender, low BMI, co-existent diseases, and low albumen levels as risk factors of increased perforation rates in hospitalized patients, especially among those admitted to the intensive care unit. In terms of indications, perforation rates have been found to be higher during procedures performed for diagnosing abdominal pain, anemia, Crohn's disease, and bleeding (21).

Perforation rates decrease with the experience of the endoscopist (3, 12). However, experience alone is not sufficient to prevent perforations due to the various risk factors discussed previously. Lohsiriwat et al. (26) stated in their study of 10,124 patients that the experience of the endoscopist did not play a significant role in reducing complication rates. In our study, the experience of the endoscopists varied between 2 and 15 years. Of all cases in which perforations were documented, two were by trainees under the control of experienced specialists, three were by endoscopists who had 5 to 10 years of experience, and two were by endoscopists who had 10 to 15 years of experience.

Clinical findings may vary due to several factors. These include time duration from the onset of perforation, degree of abdominal contamination, size and etiology of the perforation, and accompanying diseases of the patient (7, 13, 19, 26). Early surgical intervention is the gold standard approach in the presence of peritoneal irritation findings. Some research-

ers recommend emergency surgery when sub-diaphragmatic free air is detected, even in the absence of peritoneal irritation. Early and emergent surgical intervention is suggested to be the best treatment strategy to decrease rates of mortality and morbidity (26-30).

Luning et al. (8) reported 35 perforation cases in their study that consisted of 30,366 cases (0.12%); surgery was performed on all 35 patients. Seventy-four percent of the perforations occurred in the sigmoid colon, and the mortality rate was found to be 8.6%. Similarly, our mortality rate was 7.6%. In one patient who refused surgical intervention, death occurred due to sepsis. Farley et al. (27) reported their perforation rate as 0.075% (43 cases) among 57,028 patients; they treated only one patient (2%) non-surgically. Korman et al. (1) reported 37 (0.03%) perforation cases among their series of 11,6000 patients; they followed up 2 of these patients non-surgically. Factors known to increase morbidity following perforation are time of diagnosis, degree of peritoneal contamination, coexisting diseases, and size of the perforation (31). In our study, the postoperative morbidity rate was found to be 54.4% (six patients); the most common cause was wound infection.

In recent years, successful results have been reported with new developments in endoscopic techniques.

Multi-canal endoscopic tools, intraluminal or over-the-scope (OTSC) endo-clips, endo-loops, and tissue-sealing materials such as fibrin glue and partially or fullly covered self-expandable metallic stents (SEMS) are some of these new techniques (32). Endo-clip procedures have been reported in the literature since 1997, as well as successful repairs of large intestinal perforations with combinations of endo-clips and endo-loops (33-35). Also, closure of intestinal perforations with injection of fibrin glue has been reported (36). A perforation site of 30 mm has been reported to be repaired successfully with OTSC (37). Covered SEMS procedures have been used for stricture dilatation in distal colonic anastomosis (38). Aras et al. (39) reported 16 patients with colonoscopic perforation in their series; some cases were treated using minimally invasive techniques. Of 16 patients with colonoscopic perforation, 8 (50%) were treated by primary repair; 5 (31%) of these were approached laparoscopically. Bowel resection was performed in three (19%) patients and diversion in one (6%) patient. Regarding nonoperative treatment, three (19%) patients were successfully managed conservatively. Endoscopic closure of the CP was applied using a hemoclip in one (6%) patient.

In our series, we could not apply endo-clips because they were not available in our clinic at the time of our study. The most important indication for endoscopic repair is the size of the perforation site, which should be less than 10 mm (12). Although the literature indicates that it is safe, certain conditions must be met for stent placement in colonoscopic perforations. Generally, these conditions are related to the hospital facilities, including the availability of an experienced endoscopist and associated assistant team and the availability of the proper stent and equipment when required (40).

However, we believe that non-surgical follow-up should only be considered for patients who are stable and show no symptoms of peritoneal irritation. The patients should be hospitalized and followed up without oral intake, intravenous fluid support, and antibiotic prophylaxis. Because of the high risks, non-surgical follow-up should be applied in carefully selected patient groups; the possible risks should be described to patients and their families, and informed consent should be obtained. The current study is limited by its retrospective nature and non-randomized design. Also, we lacked the facilities to perform procedures such as ESD or EMR; as such, we could only assess perforation cases due to endoscopic polypectomy.

CONCLUSION

The findings from our study showed that patients older than 65 years and those with ASA scores greater than 3 are at higher risk for colonic perforation following therapeutic endoscopy. Colonoscopy is an invasive method associated with an appreciable rate of complications. Early diagnosis and treatment are necessary to reduce mortality and morbidity rates. Unexpected symptoms such as abdominal pain or distention, hypotension, and tachycardia following the procedure should trigger suspicion of colonic perforation, especially in patients identified to carry higher risks.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ş.Ç.; Design - Ş.Ç., B.G.; Supervision - H.B.; Resource - E.Ç., Ş.B.; Materials - A.G.; Data Collection and/or Processing - Ş.Ç., Ş.B.; Analysis and/or Interpretation - Y.D., B.G.; Literature Search - Y.D., Ş.Ç.; Writing Manuscript - B.G., Ş.Ç.; Critical Reviews - H.B.

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Evaluation of the Alvarado scoring system in the management of acute appendicitis

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ABSTRACT

Objective: In this study, we aimed to show the effectiveness of Alvarado score and its components to predict the correct diagnosis of acute appendicitis and to find an optimum cut-off value for Alvarado score.

Material and Methods: The patients who underwent surgical operation between January 2011 and January 2012 with the suspicion of acute appendicitis were included in the study. Their demographic and clinical features and histopathological results were retrieved from the medical records. They were divided into three groups according to their Alvarado scores. With the use of "receiver operating characteristic" curve analysis, the optimum cut-off value needed to make a correct diagnosis of acute appendicitis was determined.

Results: In all, 156 patients were included into the study. The mean age was 31.41±13.27 years. Histopathologically, acute appendicitis was detected in 125 (80.1%) patients, and negative appendectomy was found in 31 patients (19.8%). Mean Alvarado score was 6.44±1.49. There was a significant correlation between negative appendectomy and low Alvarado score ($p<0.001$). The main component of Alvarado score that makes the difference was rebound. Fever higher than 37.3°C, rebound, loss of appetite, and existence of shifting pain were statistically differential components ($p=0.042$, $p<0.001$, $p=0.045$, $p<0.001$, respectively). The rate of correct diagnosis of acute appendicitis was maximum in group 3 (100%) and minimum in group 1 (21.7%). Optimum cut-off value for Alvarado score was 7.

Conclusion: Patients with an Alvarado score of over 7 can be taken into surgical operation without the need of imaging methods.

Keywords: Acute appendicitis, Alvarado Score, cut-off value

INTRODUCTION

Acute appendicitis (AA) is the most common emergency condition requiring surgery in emergency admissions (1). Lifetime prevalence of the disease for individuals is 8% (2). Even with the frequent occurrence and the technical improvements in diagnostic modalities, the diagnosis of AA is challenging. It is mainly based on careful clinical history and physical examination (3). Many authors use imaging modalities when the diagnosis is doubtful. However, in rural areas of the country, it is difficult to evaluate the patient with ultrasonography or abdominal computed tomography under emergency conditions. Besides, unnecessary use of imaging modalities might cause a delay in diagnosis and also increase the economic burden (1, 4). Around 15%-30% of the patients who had previously undergone surgery with a diagnosis of AA were reported to have had negative appendectomy and 20% had perforation (5-8). Correct diagnosis is important to prevent perforation and negative appendectomy.

Therefore, clinical studies have aimed to find out the most cost-efficient, noninvasive, and practical diagnostic procedures. To this end several scoring systems have been proposed for AA (9). Alvarado score (AS) is the first and most widely known scoring method, the accuracy of which has been clinically approved (10). It uses mainly clinical findings and laboratory values (i.e., migration of pain, anorexia, nausea and/or vomiting, right lower quadrant tenderness, rebound, elevation of temperature ≥37.3°C, leukocytosis $\geq 10\times10^3/mm^3$, and polymorphonuclear neutrophilia ≥75%) to assess the presence of AA (3) (Table 1). It has been shown that AS prevents the delay in therapy and reduced the negative appendectomy rate (11). Although AS has a high accuracy rate, there is no sufficient study about the contribution of individual components to correct diagnosis. In this study, we aimed to show the effectiveness of AS and its components individually on accurately diagnosing patients with AA. Besides, we would like to suggest a "management algorithm" based on AS.

MATERIAL AND METHODS

This study was conducted in accordance with The Helsinki Declaration. Patients who underwent appendectomy due to AA between January 2011 and January 2012 at, Gaziosmanpaşa University School of Medicine, Department of General Surgery were included in the study. Patients who have gynecological

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pathology requiring surgical intervention with a diagnosis of AA, those whose histories could not be taken due to communication problems, pregnant patients, those taking painkillers, those who have comorbidities (such as diabetes mellitus, hypertension, and cardiac disease), and those who have incidental appendix tumors were excluded. Patients were clinically evaluated by the emergency medical team on call. Ultrasonography was requested based on physical examination and laboratory findings. In cases where the accuracy of diagnosis was uncertain, abdominal computed tomography was performed. Subsequently, the team consulted surgery for the diagnosis. Written informed consent was obtained from patients participated in this study. The operation was performed by the same surgical team laparoscopically or as open surgery. The demographic and clinical findings and histopathological characteristics were all retrieved from patient files. As were calculated retrospectively. The patients were divided into three groups depending on AS values (12).

Group 1: Patients with AS of ≤4, appendicitis unlikely
Group 2: Patients with AS of 5-7, appendicitis with moderate possibility
Group 3: Patients with AS of ≥8, appendicitis with high possibility

For individual components of AS, sensitivity, specifity, positive predictive value (PPV), and negative predictive value (NPV) were separately determined.

Statistics Analysis

For statistical evaluation, Statistical Package for the Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA) was used. For descriptive data, numeric values were given as mean±standard deviation (SD) and categorical values as rate. Data distribution was analyzed with Kolmogorov-Smirnov. If the distribution was normal, Student T test was used, and if not, Mann-Whitney U test was used. Categorical values were compared using Chi-Square Tests. Performance of AS for determining AA was evaluated using "receiver operating characteristic" (ROC) curve. The field under ROC curve and its standard error were calculated. Optimum cut-off value for AA diagnosis was found. Sensitivity and specifity rates were determined for all ASs. $p<0.05$ was accepted as statistically significant.

Table 1. Alvarado Scoring system

	Component	Score
Symptoms	Migration of pain	1
	Anorexia	1
	Nausea and/or vomiting	1
Signs	Right lower quadrant tenderness	2
	Rebound	1
	Elevation of temperature ≥37.3°C	1
Laboratory	Leukocytosis ≥10 ×10³/mm³	2
	Polymorphonuclear neutrophilia ≥75%	1
Total		10

RESULTS

Demographic and Clinical Findings

A total of 156 patients were included. Of these, 98 patients (62%) were male and 58 patients (38%) were female. Demographic and clinical features of the patients were shown in Table 2. There were 23 patients in Group 1, 86 patients in Group 2, and 47 patients in Group 3. The mean age of patients was 31.41±13.27 years. The mean AS was 6.44±1.49 in patients. Although hispathologically appendicitis was detected in 125 patients (80.1%), 31 patients (19.8%) had negative appendectomy. There was difference among AS groups in terms of average age ($p<0.001$). The post-hoc analysis showed a difference between Group 1 and Group 2. There was no difference in terms of sex between AS groups ($p=0.513$). The negative appendectomy rates in the three groups were 78%, 15%, and 0%, respectively. The difference among the groups was statistically significant ($p<0.001$).

The Efficacy of AS Components in the Diagnosis

Sensitivity, specifity, PPV, and NPV of each Alvarado components are shown in Table 3. Pain in the right lower quadrant was positive in all patients. Fever higher than 37.3°C, rebound, loss of appetite, and existence of migrating pain were the differential components that were statistically significant ($p=0.042$, $p<0.001$, $p=0.045$, and $p<0.001$, respectively).

ROC Curve Analysis and Optimum Cut-Off Value

The ROC curve for AS is shown in Figure 1. The area under the curve for AS was 0.853 (standard error (SE), 0.038; 95% confidence interval (CI), 0.779-0.927) ($p<0.001$). AS performance at each cut-off value is shown in Table 4. Cut-off value was found significant for 6 and 7 ($p<0.05$). For these cut-off values, sensitivity, specifity, PPV, and NPV with histopathological findings are shown in Table 5. ROC curve indicated that the optimum cut-off value of AS for correct diagnosis of appendicitis is 7.

Table 2. Demographic and clinical characteristics of the patients

		Group 1	Group 2	Group 3	Total	p
Patients (n/%)		23/14.7	86/55.1	47/30.1	156/100	
Gender (n/%)	Male	12/7.6	55/35.2	31/19.8	98/62.8	0.513
	Female	11/7	31/19.8	16/10.2	58 /37.2	
Age (mean±SD)		25.7±11.5	34.46±14.2	30.6±13.1	31.41±13.27	<0.001
AS (mean±SD)		3.60±0.58	6.09±0.80	8.48±0.68	6.44±1.49	<0.001
Appendicitis (-/+) (n)		18/5	13/73	0/47	31/125	<0.001

AS: Alvarado score; SD: atandard deviation

Table 3. The efficacy of Alvarado score components for diagnosis

AS components	AA+ (n)	AA- (n)	Sensitivity %	Specificity %	PPV %	NPV %	p
Migration of pain	87	10	69.6	67.7	89.6	35.5	<0.001
Anorexia	95	18	76	41.9	84	30.2	0.05
Nausea and/or vomiting	68	12	54.4	61.2	85	25	
Right lower quadrant tenderness	125	31	100	100			
Rebound	116	21	92.8	32.2	84.6	52.6	<0.001
Elevation of temperature ≥37.3°C	15	0	12	100	100	21.9	<0.05
Leukocytosis ≥10 ×10³/mm³	79	9	63.2	70.9	89.7	32.3	
Polymorphonuclear neutrophilia ≥%75	70	5	56	83.8	93.3	32	

AA: acute appendicitis; PPV: positive predictive value; NPV: negative predictive value

Table 4. Alvarado score performance at each cutoff value

Positive if greater than or equal to	Sensitivity %	Specificity %
2	100	0
3	100	3.2
4	99.2	22.6
5	96	58.1
6	80	71
*7	59.2	83.9
8	37.6	100
9	14.4	100
10	4	100

*Optimum cut-off value

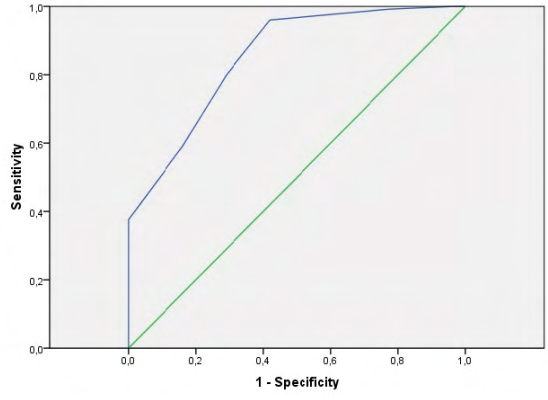

Figure 1. Clinical management strategy by Alvarado Score and probability of appendicitis

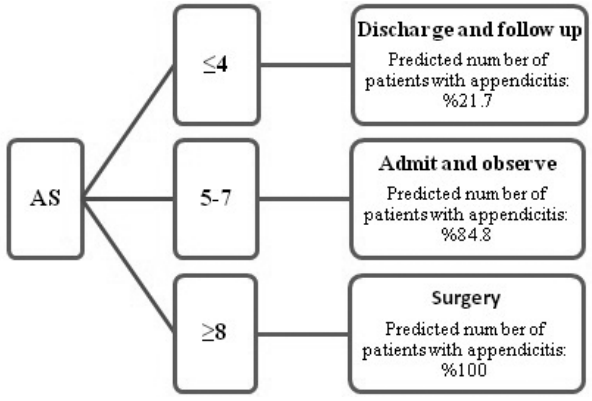

Figure 2. Receiver operating characteristic curve for diagnosis of acute appendicitis according to the Alvarado Scoring System

DISCUSSION

Acute appendicitis is the most frequent reason for acute abdomen in all age groups (12). Diagnosis can often be made solely with physical examination and laboratory findings. In suspicious cases, radiological methods are used. However, they have some disadvantages such as they are not available under rural conditions, some use radiation, and they are not cost-effective. To reduce the cost and prevent delay in diagnosis, some scoring systems such as Lintula, Madan, Ohmann, Eskelinen, De Dombal, and Alvarado were suggested. Common features of these scoring systems are that they aimed to be practical, noninvasive, and do not require much expertise to use (9). AS is a scoring system that includes clinical and laboratory findings of patient. AS has been shown to predict appendicitis accurately in many clinical studies. In their prospective study, Kariman et al. (13) evaluated AS in 300 patients who were admitted with abdominal pain and randomized them into two groups depending on their score with the cut-off value of 7. They found that AS can be used in patients with abdominal pain reliably and a score of more than 7 indicates AA possibility at the rate of 93% and a negative test (i.e., AS of ≤7) indicates unlikeliness of AA at the rate of 26%. As a result, they stated that AS is a reliable test for the diagnosis of appendicitis but insufficient to exclude the diagnosis. Chan et al. (14) found that the incidences of AA in patients with an AS of 9-10, 7-8, and ≤6 were 100%, 68%, and 5%, respectively. When AS and histopathological findings in the groups in our study were compared, AA possibility for groups shows a resemblance to the literature.

Alvarado score helps to stratify the patients who should undergo further examination, follow-up, or operation (15). The studies suggested that patients with an AS of ≤4 can be discharged without hospitalization, for those with an AS of 5-7, radiological methods can be used, and those with an AS of >7 should be operated (3, 16, 17). Yüksel et al. (12) investi-

Table 5. Alvarado score performance at cutoff values of 6 and 7 with regard to histopathology

Positive if greater than or equal to	AA+	AA-	Sensitivity %	Specificity %	PPV %	NPV %	p
6	100	9	80	70.9	91.7	46.8	<0.05
7*	74	5	59.2	83.9	93.7	33.8	

AA: acute appendicitis; PPV: positive predictive value; NPV: negative predictive value
*Optimum cut-off value

gated the reliability of AS in correct diagnosis of AA. They concluded that patients with AS of ≤4 can be discharged from emergency department with the suggestion of distant follow-up. Yildirim et al. (3) stated that patients with AS between 5 and 7 should be further examined using imaging modalities; however, only AS is not enough for the decision of surgery. Similarly, Mckay and Shepherd (18) concluded that imaging methods should be used in patients with an AS of 5-7 for diagnosis and patients with an AS of ≥7 should directly undergo operation without any more workup. Alvarado himself defends that patients with a score of ≥7 should undergo surgery. In our study, the optimum cut-off value for AS in AA diagnosis after ROC curve analysis was found to be 7. All patients with an AS of >7 were found to have histopathological appendicitis. The positive predictive value of AA for optimum cut-off value was 93.7%. Similar to ours, in the study of Pogorelić et al. (19) the optimum cut-off value for AS was 7 and the PPV for this value was 93.1%.

In our study, the negative appendectomy rate was 19.8%. This rate was found to be 32% by Menteş et al. (20), and 7% by Jo et al. (21). In the literature, there are few studies giving negative appendectomy rates for AS groups separately. In a previous study, Yüksel et al. (12) found negative appendectomy rates in the groups (with increasing order with AS score) to be 43.5%, 24.1%, and 11%, respectively. Although negative appendectomy rates were similar in our study and Yüksel et al. (12) study, it was higher than the average in the groups with AS of ≤4.

Based on our findings, we agree with the recommendations put forward in the literature. In short, patients with an AS score of ≤4 can be discharged and followed at home with the necessary information from the patient. Patients with an AS of 5-7 should be followed closely using imaging methods as they probably have AA. We believe that the patients with an AS of ≥8 can undergo operation without imaging methods (Figure 2). Through the literature data and our findings, this approach has been shown to increase the accuracy of diagnosis (especially in case of unavailability of radiological imaging), decrease the negative appendectomy rates, and provide an advantage in terms of cost and duration.

According to the results of this study, the main component of AS exhibiting the difference was rebound. Among the scoring components, fever higher than 37.3°C, rebound, loss of appetite, existence of migrating pain make positive attribution to the diagnosis. Rafiq et al. (22) reported that taking leukocytosis count, high fever, and high neutrophil count into account during decision-making may reduce the negative appendectomy rate in the patients with AA diagnosis.

Our study has some limitations. First, the study was retrospective in nature. Second, AS was evaluated only in patients who underwent operation. However, there were also some patients who presented at the emergency unit with nonspecific abdominal pain without proceeding to the operation. We have no data about their follow-up and treatment. In this study, physical examination, laboratory findings, and imaging methods were used for surgical decision-making. We have not compared AS solely with any of the radiological imaging methods. AS components were examined, but they were not effective for surgical decision-making. The results of our study showed that AS system can be used in the diagnosis of AA just like all the other diagnostic methods. The effectivity of individual AS components on making a diagnosis and defining an optimum cut-off value was defined.

CONCLUSION

Thus, there may be difficulties in diagnosis of AA sometimes and delayed diagnosis may affect treatment negatively. AS system is one of the most frequently used scoring systems. Among the scoring components, fever higher than 37.3°C, rebound, loss of appetite, and existence of shifting pain make a positive contribution to the diagnosis. We believe that patients with an AS over 7 should be operated without the use of imaging methods.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Successful management without protective colostomy in an adult patient with anorectal mal-formation

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ABSTRACT

Anorectal malformations are rare occurrences characterized by the absence or abnormal localization of the anus. Clinical manifestations can vary from mild forms that require only minor surgery to more complicated cases that must be managed with multi-staged surgery. In this report, our aim is to present the clinical characteristics, management, and treatment outcome of an adult patient with an anorectal malformation with a vestibular fistula that was successfully repaired by posterior sagittal anorectoplasty (PSARP) and to discuss the case in the light of the relevant literature. We also would like to underline the fact that primary anorectal malformations can, although rarely, be observed in adult patients. A 26-year-old female patient presented with an imperforate anus and constipation with feces passing through a fistula located at the distal part of her vagina. She was continent for solid feces, but had leakage of flatus and fecal soiling. She also had concurrent left renal agenesis. A posterior sagittal anorectoplasty was successfully performed without a colostomy. The patient was discharged uneventfully on the postoperative 8th day. The patient was fully continent during a control visit after seven years of follow-up. Posterior sagittal anorectoplasty is a technique that can be successfully used in adult patients with anorectal malformations.

Keywords: Anorectal malformation, colostomy, imperforate anus, posterior sagittal anorectoplasty, rectovestibular fistula

INTRODUCTION

Anorectal malformations (ARM) are embryonic developmental disorders characterized by an absence of the anus or the rectum opening to an abnormal anatomical location. Embryologically, the condition is caused by a developmental disorder of the cloaca and the transverse septum (urorectal septum), which separates the gastrointestinal system from the urogenital system. In the literature, the condition has been reported with a prevalence of 1 in 1500 to 5000 births (1, 2). However, different prevalences are observed in different parts of the world. In female children, a fistula usually develops into the vulva, vagina, urethra, perineum, or vestibule. In male children, the fistula develops into the scrotum or the urethra.

In 1982, De Vries and Pena described posterior sagittal anorectoplasty (PSARP) for the treatment of anorectal malformations (2, 3). Since that time, this technique has become widely accepted in the surgical treatment of anorectal malformations and is now the gold standard (4). Today, this technique is used to treat anorectal malformations observed both in neonates and pediatric patients as well as, rarely, in adults.

In this report, we would like to present a patient who was diagnosed with an anorectal malformation in adulthood and was successfully treated through surgery in light of the relevant literature.

CASE PRESENTATION

A 26-year-old female patient with mild mental retardation presented with constant constipation, gas, and defecation through the vagina. The patient, who did not seek medical assistance until this age for various reasons (family negligence, social factors, and low level of education), was brought to our outpatient clinic by her relatives.

Her physical examination revealed a distinctive developmental retardation. Her height was 137 cm, and she weighed 37 kg. She also had mild mental retardation. No pathologies were observed in her systemic examination. The perineal exam revealed an anorectal malformation with a retrovestibular fistula, and the anal canal ended in front of the hymen. During the preoperative period, the patient underwent intravenous pyelography (IVP), complete abdominal ultrasonography (USG), magnetic resonance imaging (MRI) of the whole abdomen and pelvic region, electromyography (EMG) of the perianal muscles, and barium graphy of the colon. In addition to the diagnosed anomaly, the tests revealed a left renal agenesis in the patient. The barium graphy indicated a dilatation of the sigmoid colon. Based on these

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Figure 1. Preoperative view of the patient. The absence of the anal orifice is obvious

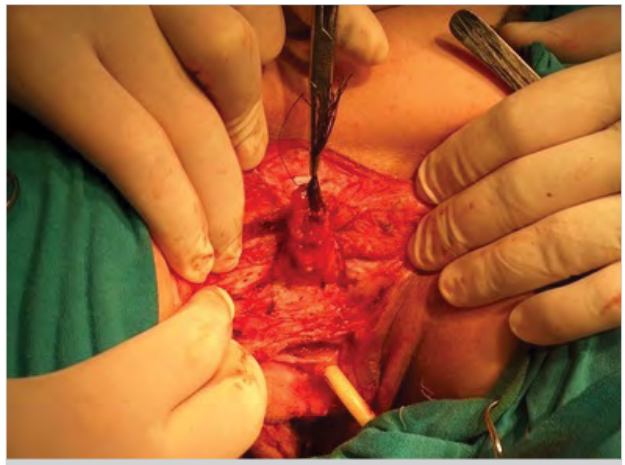

Figure 2. The rectovestibular fistula is fully revealed. The vagina is easily visible below it

Figure 3. The anterior muscle mass and construction of the anterior commissure

Figure 4. Repair of the posterior muscle complex

findings, the patient was prescribed enema and oral liquid paraffin for six months (Sokol liquid; Munir Sahin Ilac, İstanbul, Turkey).

SURGICAL TECHNIQUE

The patient was referred for pediatric surgery, urology, gynecology, psychology, and neurology consultations. Following presurgical colon preparation, under general anesthesia, a Foley catheter was placed, and the patient was brought to the jackknife position (Figure 1). Using 3/0 atraumatic polyglactin 910 (Vicryl; Ethicon, Summerville, NJ, USA), suspension sutures at 3 to 4 mm intervals were made at the mucocutaneous junction of the anus. Then, a vertical incision was made through the layers from the lower end of the sacrum to the commisura posterior over the rectovestibular fistula. The external sphincter and the muscle complex were prepared until the rectum was located in the midline (Figure 2, 3). Equal amounts of muscle were left on both sides. The rectum was separated from the vagina up to the peritoneal reflexion. After the rectum was fully released, the perineal body was repaired using 2/0 polyglactin 910 (Vicryl; Ethicon, Summerville, NJ, USA) sutures (Figure 4). First, the anterior part of the muscle group was brought together, followed by the posterior part (Figure 5). The midline of the skin was closed, and the anoplasty was completed by suturing the rectal section to be anastomized to the skin so that it remained within the borders of the external sphincter (Figure 6). During the postoperative period, the patient was not fed orally for the first week. Because no complications developed, the patient was discharged on the 10th postoperative day.

The patient was followed up for seven years. In her last control visit, she stated that she defecates regularly once a day and maintains anal continence. Her physical examination revealed no abnormalities (Figure 7). The patient did not develop anal incontinence during her seven-year follow-up.

DISCUSSION

Anorectal malformations include a number of congenital defects and various types of urinary and/or sexual malformations. A patient with an anorectal anomaly seeking medical assistance and treatment for the first time in adulthood is a rare occurrence (1, 5). These patients are usually diagnosed and treated during infancy and childhood. Although anorectal malformations usually occur as an isolated anomaly, they may also be accompanied by one or more anomalies affecting other organs. Therefore, in both pediatric and adult patients, the whole system of a patient with anorectal malformations should be very carefully examined.

Figure 5. Closure of the skin and fixation of the anus to the skin

Figure 6. Postsurgical view

Figure 7. One-year follow-up of the patient

Table 1. Krickenbeck classification of ARM

I. Major clinical groups	II. Rare/regional variants
1. Perineal (cutaneous) fistula	1. Pouch colon atresia/stenosis
2. Rectourethral fistula:	2. Rectal atresia/stenosis
i. Prostatic	3. Rectovaginal fistula
ii. Bulbar	4. H-type fistula
3. Rectovesical fistula	5. Others
4. Vestibular fistula	
5. Cloaca	
6. ARMs with no fistula	
7. Anal stenosis	

ARM: anorectal malformations

In adult patients, to determine the ideal treatment option and to achieve a satisfactory surgical result, the type and size of the defect should be carefully examined, and the anatomic structure and borders of the perineum and pelvis should be examined in detail. Also, the patient's defecation habits, which may involve constant diarrhea or constipation, are of great importance. Patients with constipation are reported to respond better to bowel training (4). Our patient also complained of constipation during the preoperative period, and barium graphy of the colon revealed a dilated rectum and sigmoid colon. To normalize the colonic calibration and regulate the intestinal function, the patient was administered an oral fluid and an enema through the fistula to soften the feces. Thus, the diameter of the sigmoid colon was brought closer to the normal size.

In all patients, direct X-rays, MCUG, fistulography, and computed tomography of the whole abdomen, MRI, USG, and colonography with a water-soluble contrast agent should be performed to detect concurrent anomalies (6). Especially, the detection of the contours of the sigmoid colon, colonic dilatation, and the length of the colon segment to be used for the repair are highly important. Even when the patient does not have any complaints related to the urinary system, the urinary system should be examined in detail in all patients. In our patient, left kidney agenesis was also detected. Pelvic MRI is important in determining anatomical differences, especially the relationship of the rectum and the sphincter. These imaging methods also reveal any additional pathologies, such as dermoid cysts or other benign tumors (7).

Although various classifications are used for this purpose, in a symposium held to resolve terminological confusion on the international level, the Krickenbeck classification presented in Table 1 gained prominence (2). According to this classification, our patient was defined as vestibular type in the major clinical group. The vestibular fistula in our patient is the most commonly observed anorectal defect in female pediatric patients with anorectal malformations (2).

Postsurgical prognosis is better in adult patients in whom the gluteal cleft is fully developed beside the sacrum and the normal gluteal muscle mass, the nerves are intact to maintain the anal reflex, and the voluntary perineal muscles are visibly con-

tractile (3). In our patient, preoperative tests revealed these structures and the anocutaneous reflex to be normal. In the literature, PSARP has been reported to be a successful method with satisfactory results in the rare adult patients with anorectal malformations (1-5). The crucial part of this surgical technique is the dissection and separation of the rectovaginal wall at full thickness. The decision to perform a colostomy should be made after meticulous consideration in adults. A colostomy may not be necessary in adult patients with optimal passages or in whom the passage is maintained at the desired level through medical methods. Thus, PSARP without a colostomy may achieve satisfactory results in selected patients. In the present patient, PSARP was performed without a colostomy, which led to an excellent result.

CONCLUSION

Anorectal malformations may be rarely observed in adulthood. In selected adult patients carefully examined in the preoperative period, the PSARP method may be successfully applied without a colostomy. In these patients, concomitant anomalies should be considered and the necessary tests should be performed. It is also important to observe the size and type of the lesion. A comprehensive preoperative evaluation will doubtlessly influence the surgical outcome. Thus, we believe that other departments, including mainly pediatric surgery, gynecology, and urology, should be involved in the systemic evaluation of adult patients with anorectal malformations.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Contributions: Concept - C.T., I.K., H.G., E.T.; Design - C.T., I.K., M.H.; Supervision - C.T., I.K., K.A.; Resource - I.K., H.G.; Materials - H.G., I.K., M.H., E.T.; Data Collection and/or Processing - C.T., I.K., H.G.; Analysis and/or Interpretation - C.T., I.K., K.A., M.H.; Literature Search - C.T., K.T., M.H., I.K., E.T.; Writing Manuscript - C.T., I.K., H.G.; Critical Reviews - C.T., I.K., M.H., K.A, E.T.

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Case Report

Development of acute cholecystitis following laparoscopic partial cholecystectomy

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ABSTRACT

In cases where the dissection of Calot's triangle is difficult during laparoscopic cholecystectomy, laparoscopic partial cholecystectomy is an alternative to total cholecystectomy to prevent bile duct damage. However, recurrent symptoms and bile duct problems associated with the remaining gallbladder tissue may develop in patients over time. The case of a 45-year-old male who underwent laparoscopic partial cholecystectomy one year previously is presented here. In the postoperative period, as a result of tests for the continuing symptoms of cholecystitis, stones and surrounding abscess were detected in the remaining gallbladder tissue, so open completion cholecystectomy was applied. In acute cholecystitis, as severe inflammation of the hilar structures does not allow safe dissection, partial cholecystectomy can be applied. However, in these patients, there is a risk of recurrence of cholecystitis symptoms and the development of biliary pancreatitis and choledocolithiasis because of the remaining tissue. Therefore, it should not be forgotten that endoscopic and/or surgical intervention may be necessary at least in some patients.

Keywords: Laparoscopic cholecystectomy, partial, subtotal, completion, acute cholecystitis

INTRODUCTION

Open or laparoscopic partial cholecystectomy has been reported to be a safe and effective operation as an alternative to total cholecystectomy in cases where intraoperative findings or variations in anatomy do not allow the safe dissection of Calot's triangle (1, 2). It is known as subtotal cholecystectomy. It is indicated when the bile duct structures cannot be evaluated because of inflammation in severe acute cholecystitis or necrotizing or gangrenous cholecystitis (1, 2). The majority of the gallbladder is removed, and a part of the neck section or gallbladder posterior wall is left in place depending on the inflammation (3). As there may be postoperative minor symptoms that can be tolerated, recurrent acute cholecystitis symptoms may lead to significant problems such as choledocolithiasis or persistent biliary fistula (4).

Even if partial cholecystectomy is technically possible, the ideal procedure is the total removal of the gallbladder (5-7). As new stones may form in the attachment of the gallbladder to the choledochus, the amount of remaining tissue may cause stump cholecystitis, choledocolithiasis, or persistent biliary colic (5).

The case of a patient with continuing symptoms after laparoscopic partial cholecystectomy is presented here, and as cholecystitis and an adjacent intra-abdominal abscess has developed in the gallbladder, completion cholecystectomy was performed.

CASE PRESENTATION

A 45-year-old male underwent laparoscopic cholecystectomy at another clinic 12 months previously. Despite the operation, complaints of abdominal pain and nausea continued in the postoperative period. As the complaints increased in the previous month, tests were performed. On abdominal ultrasonography, a solid mass of calcifications was determined in the lateral left lobe of the liver. Computed tomography (CT) was performed, and a 6 cm×6 cm cystic lesion was seen in segment 4-5 of the liver around the metallic clips adjacent to the gallbladder fossa, and to the medial of this lesion, a second multiseptal cystic lesion of 7 cm×6 cm was seen in the first part of the duodenum wall and stomach antrum (Figure 1). Adjacent to the lesions, an area of 2 cm×3 cm calcification was seen (Figure 2). It was anticipated that the patient would undergo total cholecystectomy because there could be a hydatid liver cyst or intra-abdominal infection because of gallbladder stones scattered in the abdomen. The patient was operated on with these findings. In the exploration, a mass was revealed over the omentum between the liver and the small curvature of the stomach. When adhesions were opened, abscess drainage from this area was performed. A 3 cm stone was seen in the Hartmann's pouch of the gallbladder inside the open lumen. It was understood that a partial cholecystectomy had been performed on the patient. A completion cholecystectomy was performed, and the patient was discharged on the 4th day postoperatively without any medical problem.

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DISCUSSION

In acute cholecystitis, as severe inflammation does not allow the safe dissection of the hilar structures, partial cholecystectomy can be performed (1, 2). In the study by Kaplan et al. (1) who compared subtotal cholecystectomy with open cholecystectomy in patients with complicated cholecystitis, the rate of serious complications (damage to the common hepatic canal, vascular damage, and gastrointestinal damage) was found to be higher in the patients who underwent open cholecystectomy (7.9% vs. 0%). To avoid complications that may develop in cases of complicated cholecystitis demanding total cholecystectomy, subtotal cholecystectomy was recommended, and the conclusion that it could be applied as a safe alternative was reached. In a meta-analysis by Elshaer et al. (8), indications for subtotal cholecystectomy were severe cholecystitis (72.1%), cholelithiasis in liver cirrhosis and portal hypertension (18.2%), and empyema or perforated gallbladder (6.1%), and of these cases, re-operation was required in 1.8%. From this meta-analysis, the conclusion that subtotal cholecystectomy is an important tool for use in difficult gallbladders that achieves morbidity rates comparable to those reported for total cholecystectomy in simple cases was reached. However, besides the advantages obtained in the early period by not dissecting hilar structures in these patients, there is a risk of cholecystitis symptoms recurring in the future, which is directly related to the amount of remnant gallbladder and the risk of the development of biliary pancreatitis and choledocolithiasis. Therefore, in some cases where partial cholecystectomy was performed, re-operation may be necessary for the remnant gallbladder (5, 9).

In the case presented here, the symptoms of cholecystitis continued in the postoperative period, for which antibiotherapy was received twice at different clinics. However, as acute cholecystitis developed in remnant gallbladder after the partial cholecystectomy, an adjacent intra-abdominal abscess formed. There was a lack of knowledge of the patient's previous operations, so the decision for surgery was taken on the assumption of the abscess and mass in the gallbladder. After intraoperative evaluation, a confirmed diagnosis was made, and a completion cholecystectomy was performed. When there are recurrent symptoms in patients who underwent partial cholecystectomy, evaluation should be made considering these complications.

When the diagnosis is preoperatively made, laparoscopic excision of the remaining tissue can be planned. However, there is a high possibility that the operation will need to be changed to open surgery because of potential adhesions (9). In the case presented here, there was a very low possibility of a laparoscopic operation because of adhesions and the location of the abscess.

CONCLUSION

It must be kept in mind that complications may develop associated with the remaining tissue in cases of partial cholecystectomy, and therefore, surgical intervention may be necessary.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

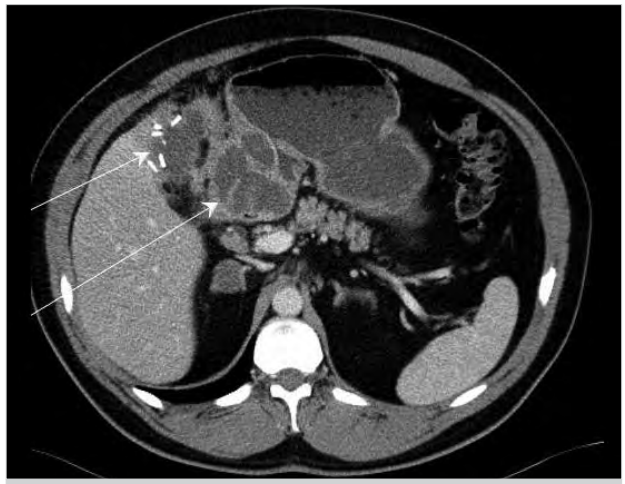

Figure 1. Abscess areas adjacent to the remnant gallbladder

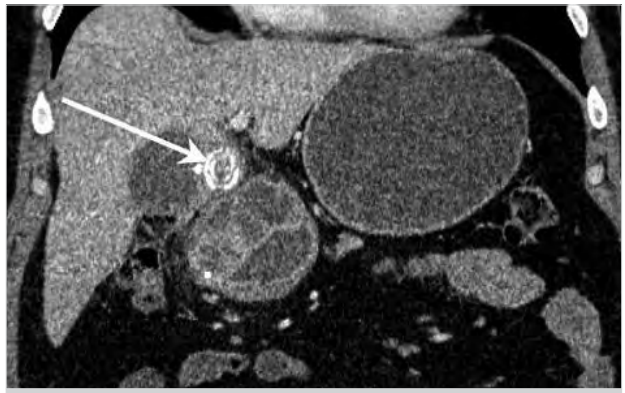

Figure 2. Stones in the remnant gallbladder and adjacent abscess areas

Peer-review: Externally peer-reviewed.

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Case Report

Two pseudotumor cases mimicking liver malignancy

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ABSTRACT

Inflammatory pseudotumor of the liver is a rare benign tumor that can be confused with malignant tumors of the liver. It is usually diagnosed after pathologic evaluation of the resected lesion. If a mass lesion in the liver is suspicious for malignancy on radiologic evaluation then surgical resection is planned for suitable patients rather than a biopsy. Inflammatory pseudotumors are similar to malignant tumors on macroscopic assessment, but microscopically they are characterized by the presence of inflammatory cells. In case of clinical or radiologic suspicion, the lesion is biopsied and once the diagnosis of inflammatory pseudotumor is made the lesion is managed by conservative-medical treatment. It must be kept in mind as part of differential diagnosis to avoid unnecessary surgery.

Keywords: Liver tumor, inflammatory pseudotumor, liver resection

INTRODUCTION

Inflammatory pseudotumor of the liver (IPT) is a rare benign tumor that can be confused with malignant liver tumors. The most frequent occurrence sites except the liver include the central nervous system, intestine, omentum, orbit, urinary bladder, breast, pancreas, lymph nodes, skin and soft tissue (1). Macroscopically, the lesions may mimic malignancy, the nodules can be solitary or multiple. Their size may reach up to 25 cm. Microscopically, they are characterized by fibrovascular tissue proliferation, spindle-shaped cells, myofibroblasts, and mixed inflammatory cells (plasma cells, lymphocytes, histiocytes, eosinophils) (2). A retrospective analysis of 403 patients operated on for focal liver lesions revealed an IPT incidence of 0.7% (3). There are fewer than 300 cases reported in the literature (4). In this article, we present two patients who have undergone right and left hepatectomy, respectively, with a pre-operative diagnosis of malignancy who were diagnosed with inflammatory pseudotumor of the liver on pathologic examination.

CASE PRESENTATIONS

Case 1

Fibronecrotic granulomatous inflammation mimicking hepatocellular carcinoma- underwent right hepatectomy.

A 58-year-old man who has been followed-up for type 2 diabetes mellitus for eight years underwent abdominal ultrasound for evaluation of a 5 kg weight loss within the past 6 months that revealed a 5 cm mass in the 5th segment of the liver. His abdominal computed tomography (CT) and magnetic resonance imaging (MRI) revealed radiological findings suggesting hepatocellular carcinoma (HCC) with a hypervascular 5 cm mass in the 5th segment extending to the 6th segment with early washout (Figure 1, 2). The patient was planned for right hepatectomy.

Laboratory findings: Aspartate aminotransferase (AST): 12 U/L, alanine aminotransferase (ALT): 8 U/L, gamaglutamyl transferase (GGT): 19 U/L, alkaline phosphatase (ALP): 85 U/L, Total bilirubin (T.Bil): 0.6 g/dL, direct bilirubin (D.Bil): 0.1 mg/dL, INR: 0.9, tumor markers: CA 19-9: 2.7 U/mL, AFP: 2,6 ng/mL, Hepatitis markers: HBsAg: (-), Anti Hbs: (+), Anti HCV: (-).

His positron emission tomography (PET-CT) showed heterogeneous moderately increased pathological fluorodeoxyglucose (FDG) uptake in the 5th-6th segments of the liver (early SUVmax: 4.6, late SUVmax: 5.8). The partial increase in FDG uptake in late images was interpreted in favor of HCC (Figure 3).

The patient underwent right hepatectomy after obtaining informed consent. He was followed-up in the intensive care unit for 12 days due to lung infection and atelectasis in the postoperative (PO) period. Oral intake was started on the 3rd PO day. He was admitted to the clinic on the 12th PO day with

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approximately 1000cc of ascites drainage per day. The ascites was kept under control with albumin, furosemide, spironolactone and enteral hyperalimentation. His bilirubin levels increased starting from the 2nd PO day. His laboratory results on PO day 12 were as follows: AST: 113 U/L, ALT: 82 U/L, ALP: 375 U/L, GGT: 567 U/L, T. Bil:11 mg/dL, D. Bil: 6 mg/dL, INR: 1.3 Total Protein (T.Pro): 4.4 g/dL, Albumin (Alb): 2.9 g/dL. The bilirubin level peaked at 20 mg/dL (AST: 212 U/L, ALT: 172 U/L, ALP: 261 U/L, GGT: 295 U/L) on the 30th PO day. His MR and MR cholangiography (MRCP) did not reveal intrahepatic or extrahepatic biliary dilation. There were ischemic changes in the 4th segment and the caudate lobe. The patient was considered as hepatic insufficiency at regeneration stage. The bilirubin levels began decreasing after reaching 20 mg/dL.

Figure 1. First patient, HCC appearance in CT
CT: computed tomography; HCC: hepatocellular carcinoma

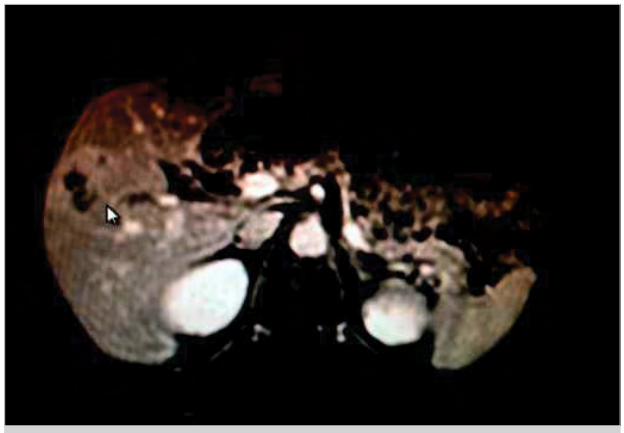

Figure 2. First patient, HCC appearance in MRI
MRI: magnetic resonance imaging; HCC: hepatocellular carcinoma

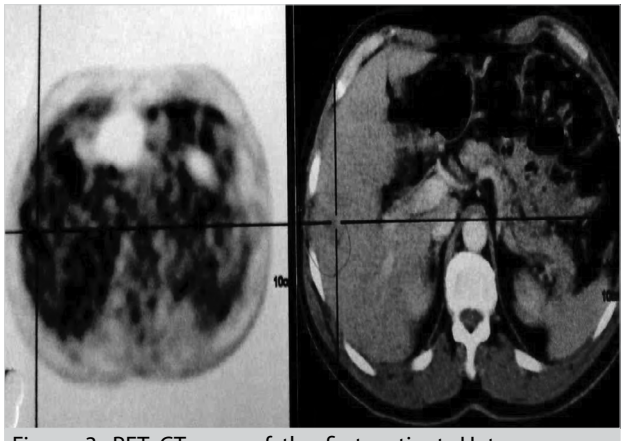

Figure 3. PET CT scan of the first patient: Heterogeneous moderate increased pathologic FDG uptake in the 5th-6th segments of the liver (Early SUVmax: 4.6, Late SUVmaks: 5.8). Interpreted as HCC
PET CT: positron emission tomography computed tomography; FDG: fluorodeoxyglucose; HCC: hepatocellular carcinoma

The patient was discharged on the 36th postoperative day. His biochemical parameters were completely normal in the second month follow-up. The patient is being followed-up for one year with no additional problems.

Pathology: The patient's pathology evaluation showed fibronecrotic granulomatous inflammatory reaction (Figure 4). The further evaluation for infectious and granulomatous diseases did not reveal any specific etiology.

Case 2

Xanthogranulomatous inflammation with cholangitis mimicking cholangiocellular carcinoma- underwent left hepatectomy.

A 53-year-old male patient was admitted to the emergency department with complaints of jaundice, abdominal pain and fever, and was diagnosed with cholangitis. His past medical history included coronary bypass operation 7 years ago and insulin-dependent diabetes mellitus for 10 years.

Laboratory findings: White blood cell (WBC): 4600, Hematocrit (Hct): 42%, T. Bil: 10.4 mg/dL, D. Bil: 5.9 mg/dL, AST: 143 U/L, ALT. 228 U/L, ALP 257 U/L, GGT: 959 U/L, INR: 0.8, CA19-9: 1254 U/mL.

Our case presented with cholangitis and was initially evaluated as choledocholithiasis-associated jaundice. The emergency US revealed intrahepatic biliary dilation mainly in the left lobe, the common bile duct was 6.3 mm in diameter, the gallbladder was contracted. His MR-MRCP showed distal common bile duct benign stricture, impacted stone, intrahepatic

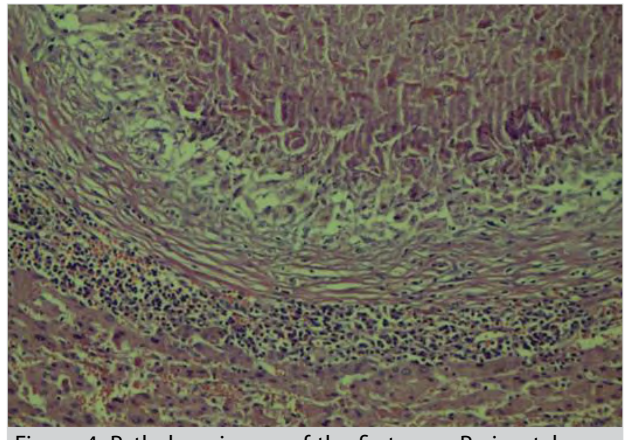

Figure 4. Pathology image of the first case: Periportal areas enlarged due to inflammation. Fibronecrotic granulomatous foci associated with bile ducts and progressing into the parenchyma are observed. Different sized foci form aggregates (HE x100).

biliary dilation, and abscess mass in the left lobe (thought to be secondary to cholangitis). An endoscopic retrograde cholangiopancreatography (ERCP) was performed, with abundant sludge and microcalculi drainage following endoscopic sphincterotomy. There was no stricture that obstructed contrast passage (contradictory to MRCP findings). Intrahepatic bile ducts could not be evaluated in detail. Bilirubin values and cholestasis enzymes were slightly decreased, but there was no significant improvement. When the patient was assessed further by CT scan, the contrast enhancement pattern of the mass was found to be consistent with cholangiocellular carcinoma (Figure 5, 6). The PET-CT showed heterogeneous, intense pathologic FDG uptake (SUVmax: 17.4) with biliary tract dilation in nearly the entire left hepatic lobe. The right lobe was preserved and the findings were interpreted as cholangiocellular carcinoma (Figure 7).

He was scheduled for left hepatectomy after obtaining informed consent. In the operation, there was extensive inflammation in the liver as well as lesions suggesting metastatic nodules in both the left and right hepatic lobes. The frozen-section evaluation of these nodules did not show apparent malignancy, nevertheless, since the suspicion of malignancy persisted, numerous biopsies were obtained and the operation was terminated. Since malignancy could not be ruled out even on biopsy materials, left hepatectomy was performed one week later.

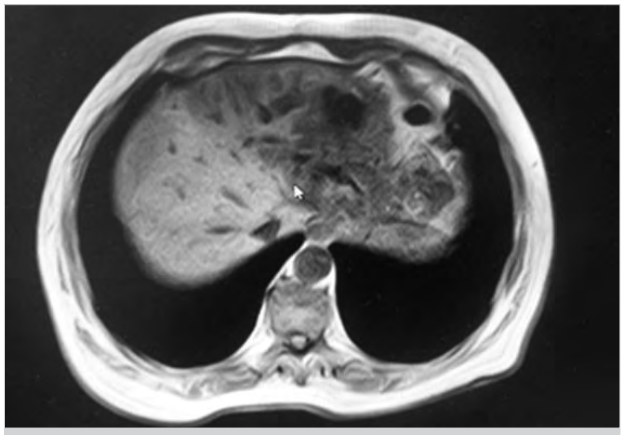

Figure 5. MR-MRCP in the second patient. A mass accompanied by 3 x 2 cm perfusion defect in the 4a segment, with a significant pre-mass IHBD dilation. Findings consistent with central dilated cholangiocellular carcinoma or focal bile duct dilation due to Caroli disease. Common hepatic and common bile duct are normal. Right IHBD are normal.

MR-MRCP: magnetic resonance-magnetic resonance cholangiopancreatography; IHBD: intrahepatic bile ducts

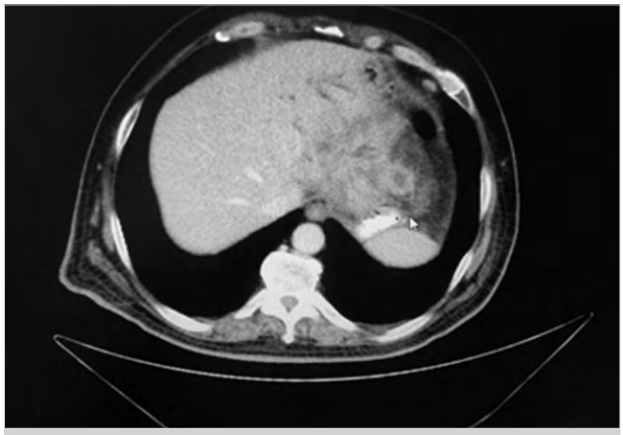

Figure 6. Abdominal CT-CT angiography of the second patient: 3 cm hypodense area in segment 4a accompanied by marked IHBD dilation in the left lobe

CT: computed tomography; IHBD: intrahepatic bile ducts

Pathology: Pathologic evaluation was concluded as inflammatory pseudotumor secondary to cholangitis.

General surgery follow-up

Preoperative final laboratory values: AST: 106 U/L, ALT: 66 U/L, GGT: 184 U/L, ALP: 362 U/L, T. Bil: 14 mg/dL, D.Bil: 9 mg/dL, T.Pro: 6.5 g/dL, Alb: 2.2 g/dL, INR: 1.1, Ca 19-9: 362 U/mL, Hct: 27%, WBC: 9000.

The patient was planned for left hepatectomy with a presumptive diagnosis of cholangiocellular carcinoma.

First surgery: The patient was taken to surgery after obtaining informed consent. A small amount of ascites was detected on exploration and samples were taken for cytopathological and biochemical analyzes. The liver was completely inflamed with tumor nodules in the left lobe 2nd and 4th segments, and there were a few 1-cm nodular lesions suggesting metastasis in the right lobe 5th and 7th segments. Biopsies were obtained from segments 2, 3, 5 and 7. On frozen-section examination, the lesions were not evaluated as malignancy but as fibrosis. Since intrahepatic metastases could not be ruled out, the operation was terminated to await paraffin section examination results, which revealed active chronic inflammation, fibrosis, biliary duct proliferation, cholangitis, lobular distortion, presence of bile pigment in hepatocytes, and balloon degeneration. Ascites evaluation did not reveal any specific feature.

Conclusion: The findings were interpreted as changes secondary to bile duct obstructive neoplasia. Malignancy could not be ruled out.

As the samples obtained from the right liver did not show signs of metastasis, and the possibility of malignancy of the left lobe mass continued, the patient was scheduled for left hepatectomy one week later. Left hepatectomy was performed in the inflamed and edematous liver.

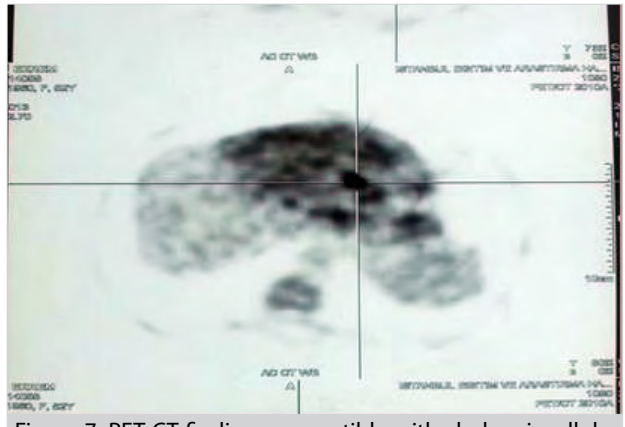

Figure 7. PET CT findings compatible with cholangiocellular carcinoma of the second patient.

PET CT: positron emission tomography computed tomography

Second pathology: On gross examination, there were extensive nodular infiltration areas of 0.5-1cm in size with nodules up to 6 x 3 cm in segment 3, and of 5 x 3 cm in segment 5. The surgical margin was negative by 1.5 cm.

Microscopic findings: Active chronic cholangitis with extensive bile duct destruction, xanthogranulomatous inflammation-inflammatory pseudotumor findings replacing the parenchyma (Figure 8), chronic pericholecystitis forming lymphoid aggregates in the cholecystectomy material, reactive hyperplasia in dissected lymph nodes.

Clinical course: The patient was followed-up in the intensive care after both operations, and remained there for 2 days after the first surgery and 3 days after the second. He developed wound infection and ascites drainage in the postoperative period. Wound infection was controlled with antibiotics, ascites drainage was treated with albumin, furosemide, and spironolactone. There was no specific finding in his outpatient work-up.

DISCUSSION

The etiology of inflammatory pseudotumor of the liver include infectious agents (*Bacteriodes caccae, Actinomyces, Klebsiella, E. coli*), autoimmune hepatopancreatobiliary diseases (IgG4 sclerosing cholangitis), and systemic granulomatous diseases (tuberculosis, sarcoidosis) (5).

Patients present with complaints of fever, abdominal pain, weight loss, jaundice (secondary to obstruction of intra- or extra-hepatic bile ducts by the inflammatory mass). Laboratory and radiological findings are not very specific for differential diagnosis. Biopsies may be performed to avoid unnecessary surgical intervention in suspicious contrast enhancement of the liver lesion, and in positive laboratory findings of infection, inflammation, or autoimmune diseases (6). Biopsy has complications such as bleeding, tumor seeding, and infection. Therefore, masses suggesting liver malignant tumors with typical contrast-enhancement pattern are treated by resection without biopsy. Biopsies are performed due to suspicion in masses that do not suggest malignancy by contrast-enhancement pattern (4).

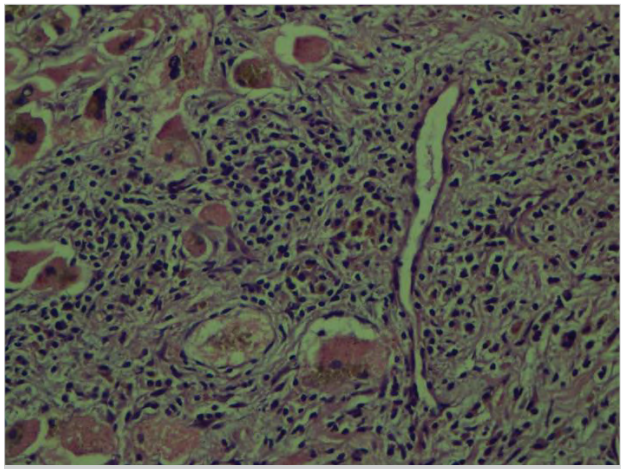

Figure 8. Pathologic view of the second patient. Diffuse cell infiltration consists of lymphocytes, plasmocytes, eosinophils and neutrophil polymorphs in each area. Cell infiltration is concentrated around periportal areas and ducts, and extends into the parenchyma. Bile ducts are proliferated. Bile pigment accumulation and balloon degeneration are evident in hepatocytes. Polymorphs form aggregates in several areas (HE x400).

Patients diagnosed with pseudotumor on biopsy are treated with antibiotics, non-steroidal anti-inflammatory drugs, and corticosteroids. Constitutional symptoms and lesion regression are closely monitored (4, 7). Surgery is considered if conservative treatment fails (persistent fever, tumor enlargement) or in case of hepatic hilum involvement, jaundice or portal hypertension (8).

In most cases, IPT is confused with other malignant tumors and is diagnosed pathologically after surgery. Surgery should be considered in case of diagnostic uncertainty and ongoing tumor suspicion (7).

Although several reports indicate no recurrence after surgical resection, there are reports on malignant transformation and recurrences even 4-7 years later (7, 10).

CONCLUSION

Inflammatory pseudotumor of the liver is a very rare condition that can be confused with malignant tumors. It is associated with infectious, inflammatory and autoimmune diseases. The tumor appearance in the liver shows contrast-enhancement pattern similar to other malignancies. IPT should be kept in mind as part of differential diagnosis in patients with systemic symptoms, laboratory or imaging findings, and unnecessary surgery should be avoided by biopsy in case of suspicion. They should be treated with conservative medical treatment (antibiotics, anti-inflammatory drugs, corticosteroids) and surgery should be applied in unresponsiveness to treatment and suspicion for malignancy. Most cases are diagnosed with pathologic evaluation after resection of a mass due to suspicion of malignancy. There are reports of recurrence and long-term malignant transformation (10), thus patients should be followed-up closely.

Informed Consent: Written informed consent was obtained from patients who participated in this case.

Peer-review: Externally peer-reviewed.

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Case Report

Intussusception of the bowel in adults: two different cases

Ergin Arslan[1], Kasım Çağlayan[1], Mesut Sipahi[1], Oktay Banlı[1], Fatma Gündoğdu[2], Sevinç Şahin[3]

ABSTRACT

Intussusception in adults is considered an unusual condition accounting for 5% of all cases of intussusceptions and almost 1%–5% of all cases of bowel obstruction. We present two cases of patients with a complaint of abdominal discomfort and concomitant vomiting who are 43 and 44 years old. Ileocecal intussusception was diagnosed by computed tomography. One patient underwent open whereas the other underwent laparoscopic right hemicolectomy and ileotransversostomy. A histopathological study revealed lipoma in the first case and adenocarcinoma in the second. We described the diagnosis and treatment of intestinal intussusception in adults.

Keywords: Adults, intussusception, diagnosis, treatment

INTRODUCTION

Intussusception is defined as invagination of an intestinal segment with its mesentery as a result of peristalsis into the intestinal lumen. In most cases, the causes of colic intussusception in adults are malignant disease, whereas the causes of small bowel intussusception are frequently benign (lipoma, polyps, adenomas, and Meckel's diverticulum) (1). It was first defined in 1674 by Barbette and Sir Jonathan Hutchinson was the first to operate on a child with intussusception in 1871 (2). Intestinal intussusception in adults is considered as an unusual pathology and represents 5% of the total cases of intestinal intussusception (children and adults) and 1%–5% of all cases of intestinal obstruction (3). Intussusceptions are classified along with their locations into four categories: enteroenteric, colocolic, ileocolic, and ileocecal (4).

Computed tomography (CT) is the most sensitive diagnostic method for intussusceptions. All researchers report that surgery is the most effective treatment for adult intussusceptions (5). We described the diagnosis and treatment of intestinal intussusception in adults.

CASE PRESENTATIONS

Case 1

A 44-year-old man was admitted to the emergency department with three months history of intermittent lower right abdominal pain and nausea. He also had a history of obstipation and constipation. These symptoms worsened over the past three days. He had no operation history. There was no familial history of any disease. On physical examination, the abdomen was minimally distended and tender. In the right lower quadrant, an approximately 8 cm diameter mass was palpated with a deep palpation. The results of routine laboratory examinations were within the normal limit. The abdominal X-ray showed dilated loops of the small intestine, which was indicated as an obstructive pattern. After resuscitation, a CT scan was performed, which showed dilatation of small intestine because of ileocecal invagination. On exploratory laparotomy, an ileocecal intussusception was found (Figure 1). After manual reduction, a 6-cm diameter properly limited mass was palpated in the cecum (Figure 2). Right hemicolectomy and end-to-side ileotransversostomy were performed. The postoperative duration was uneventful, and he was discharged seven days after surgery. On the gross and histopathological examination of the resected cecum, a well delineated and 6.2 cm × 5.1 cm × 4.4 cm lipomatous neoplasm was detected.

Case 2

A 43-year-old man was admitted to the general surgery clinic with a diagnosis of intussusception from a gastroenterology outpatient clinic. He had a history of obstipation, constipation, and intermittent right quadrant abdominal pain. There was no weight loss in the patient. The results of routine laboratory examinations were within the normal limit. The abdominal X-ray showed non-dilated loops of the small intestine. Abdominal CT revealed cecum distention and cecal wall thickening, which were suggestive of inflammation in the cecum wall and ileocecal invagination (Figure 3a, b). An intense hypodense appearance was observed in the lumen of the cecum. There was no evidence of complete obstruction

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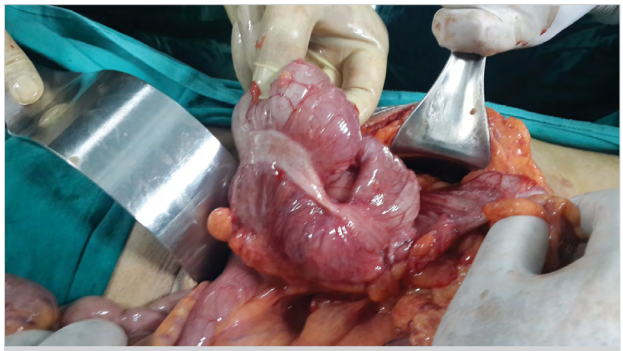

Figure 1. An ileocecal intussusception

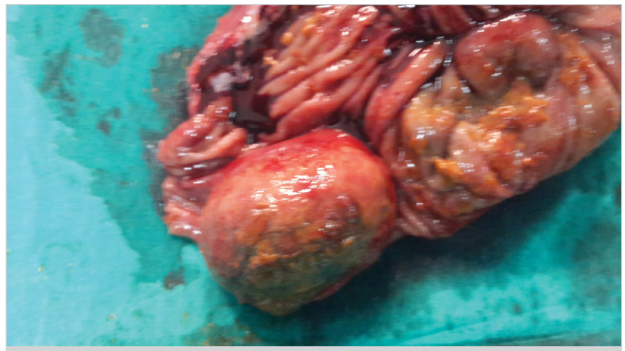

Figure 2. Lipoma causing intussusception

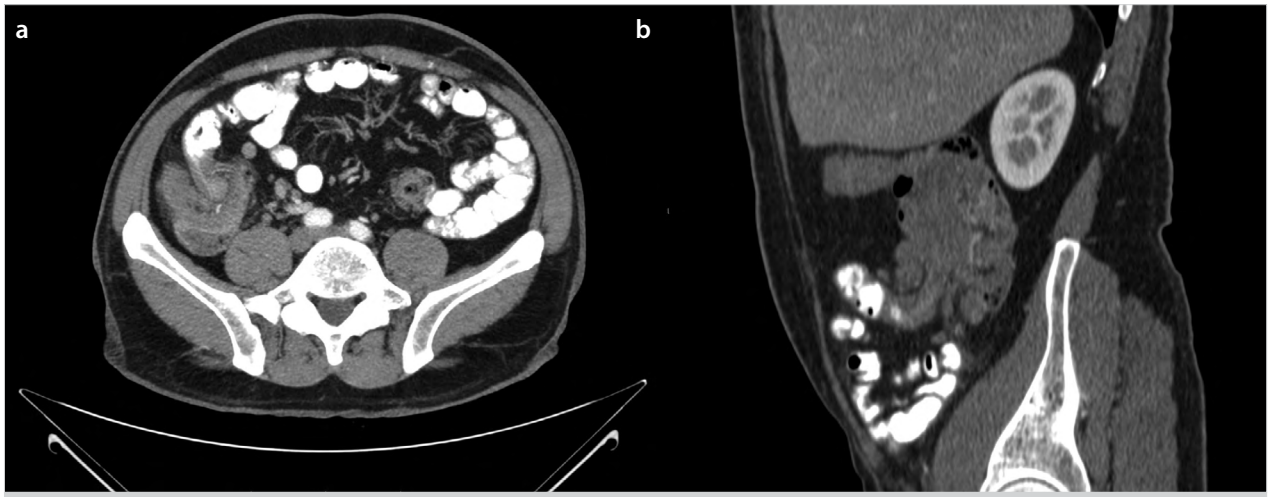

Figure 3. a, b. An ileocecal intussusception on computed tomography examination

in the patient, and colonoscopy was performed. An ulcerated mass in the lumen of the ascending colon and cecum was observed. A biopsy was taken. The biopsy confirmed the diagnosis of adenocarcinoma. Laparoscopic right hemicolectomy and ileotransversostomy was performed. The postoperative duration was uneventful, and he was discharged seven days after surgery. On the gross and histopathological examination of the resected cecum and ascending colon, a 6.5 cm × 4.8 cm × 2.2 cm tumoral lesion with irregular margins and four positive lymph nodes were detected. Mucinous adenocarcinoma was reported. The patient was classified as T3N2a (according to TNM classification stage 3 B) and adjuvant chemotherapy was administered.

DISCUSSION

Abdominal distension and tenderness are common physical findings in intussusception. Abdominal mass, tenderness, and hemoglobin positive stools are the classic triad of intussusception, but these are rarely found in adults. Blood loss or a palpable mass are present in a minority of the cases. Symptoms can be acute, intermittent, or chronic. In this study, the findings of intermittent obstruction were present in both cases. The clinical presentation in adult intussusceptions is often chronic, and most patients present with non-specific symptoms that are suggestive of intestinal obstruction. The symptoms in cases of adult intussusception are so non-specific that a clinical diagnosis beyond bowel obstruction is rarely made before surgery (6).

Obtaining the complete history and performing a physical examination are important. In the diagnosis of intussusception in adults, imaging modalities are essential. Although abdominal ultrasound and double-contrast radiographs could be used, abdominal CT is the most commonly used imaging modality because of the diagnostic appearance (7). On CT, intussusception appears as a "sausage-shaped" mass in the longitudinal axis and as a "target" mass in the transverse axis. Also, a thickened bowel wall with loss of facial plan and a reniform (pseudokidney) or thick-walled bilobulated image may be suggestive of vascular failure and helps in the decision of emergency surgery. Ischemic necrosis of the affected bowel segment is very important in selecting the optimal treatment decisions. Although it may be easily diagnosed with CT and magnetic resonance imaging, the primary reason is to reveal the condition of the intestines and the affected bowel segment (8).

Barbiera et al. (9) did not recommend hydrostatic reduction of intussusception because of the high likelihood of malignancy in adults, and instead, they recommended laparotomy. Authors suggest that surgical resection without reduction should be the standard treatment in adults because approximately 50% of adult intussusceptions are associated with malignant lesions. Simple reduction is recommended only in idiopathic intussusceptions where no pathological underlying lesion is present (10). The choice of using a laparoscopic or open procedure depends on the clinical condition of the patient and, in particular, the experience of surgeon with laparoscopic procedures.

CONCLUSION

In adults, intestinal intussusception represents a rare cause of intestinal obstruction. Clinical and paraclinical diagnostic

methods used in intestinal intussusception contribute to act quickly and perform limited intestinal resections. Tumors of the terminal ileum, cecum, and ascending colon represent possible causes of progressive intestinal intussusception.

Informed Consent: Written informed consent was obtained from patients who participated in this case.

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Author Contributions: Concept - E.A.; Design - E.A., K.Ç.; Supervision - K.Ç., M.S., O.B.; Data Collection and/or Processing - E.A., F.G., S.Ş.; Analysis and/or Interpretation - E.A., K.Ç.; Literature Review - E.A., F.G., S.Ş.; Writer - E.A., K.Ç.; Critical Review - K.Ç., O.B.

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Case Report

Lumbar (Petit's) hernia: A rare entity

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ABSTRACT

Lumbar hernias are rare and diagnostically challenging for surgeons. We present the case of a middle-aged patient who presented with swelling in the left back. Subcutaneous lipoma was included in the differential diagnosis. Following diagnostic studies, computed tomography confirmed left lumbar hernia. Elective surgery was performed, and the results revealed Petit's hernia. The hernia was repaired with mesh.

Keywords: Lumbar hernia, Grynfeltt hernia, Petit's hernia

INTRODUCTION

Lumbar hernias are rare entities. Because of their rarity and complex anatomical location, they can pose a formidable challenge to surgeons. The challenges start with diagnosis and continue to the selection of treatment (1, 2). In this report, our aim is to highlight the topic, present a case of Petit's hernia, and discuss anatomical information and management strategies under the guidance of literature reviews.

CASE PRESENTATION

A 52-year-old man was admitted to the general surgery clinic with a swelling in his back. His medical history included chronic obstructive lung disease. Surgical history included lumbar disc hernia surgery six years ago, diaphragm repair with left thoracotomy following trauma three years ago, and right inguinal hernia repair one year ago. Physical examination revealed a palpable, slightly tender mass 5 cm in diameter in the left back below the 12th rib. The remainder of his physical examination was normal. Laboratory analyses, including tumor markers, were within normal limits. Computed tomography (CT) revealed a herniated mass extending from the lumbar space to the subcutaneous area in the left posterolateral abdominal wall (Figure 1). Considering these findings, surgical treatment was planned, and the patient (in the prone position) was electively operated on under general anesthesia. An incision was made over the mass. The latissimus dorsi muscle was retracted superiorly and the herniated fatty tissue protruding from the inferior lumbar space was exposed (Figure 2). The diagnosis of Petit's hernia was confirmed. After invagination of the herniated mass, continuous 0 polyglactin sutures were placed. A polypropylene mesh was placed over the area. The postoperative period was uneventful, and the patient was asymptomatic at the 3-month follow-up.

DISCUSSION

The lumbar region is the region of the back lateral to the vertebral region and between the rib cage and pelvis. Its borders are formed medially by the erector spinae muscles, laterally by the external oblique muscle, superiorly by the 12th rib, and inferiorly by the iliac crest. The anatomical boundaries of the inferior and superior lumbar spaces were described by Petit and Grynfeltt in 1783 and 1866, respectively (1, 2). The margins of the inferior lumbar (Petit's) triangle consists of the iliac crest, the margins of the latissimus dorsi muscle, and external abdominal oblique muscles. The internal abdominal oblique muscle is observed at the floor of the inferior lumbar triangle. Borders of the superior lumbar (Grynfeltt) triangle are formed medially by the quadratus lumborum muscle, laterally by the internal abdominal oblique muscle, and superiorly by the 12th rib. The floor of the superior lumbar triangle is formed by the transversalis fascia, and the roof is filled by the external abdominal oblique muscle (1, 2).

Petit's hernia is described as herniation of retroperitoneal fat through the aponeurosis of the internal abdominal oblique muscle between the erector spinae muscles in the inferior lumbar triangle. The neck of this hernia is usually large, and therefore, it has a lower risk of strangulation than other hernias (1). Grynfeltt hernia is described as herniation of retroperitoneal fat through the aponeurosis of the transversalis muscle between the erector spinae muscles and internal oblique muscles in the superior lumbar triangle (2).

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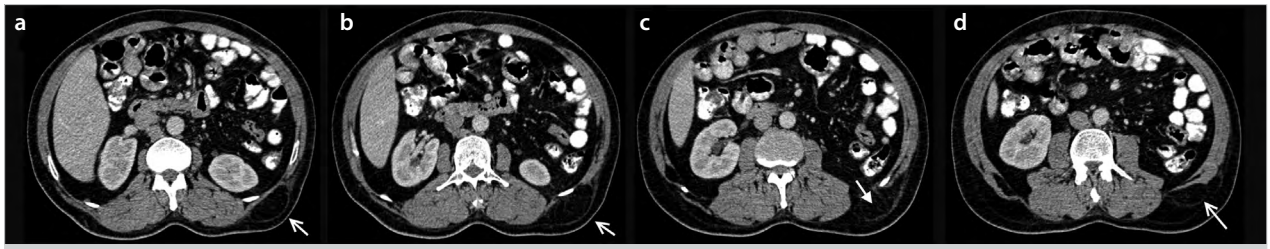

Figure 1. a-d. CT scan of the patient showing a herniated mass extending from the abdomen to the left posterolateral abdominal wall. Four CT images with 1.5-cm intervals starting from (a) to (d). White arrows in (a, b, d) show hernia. Full white arrow in (c) shows herniation through the lumbar area

CT: computed tomography

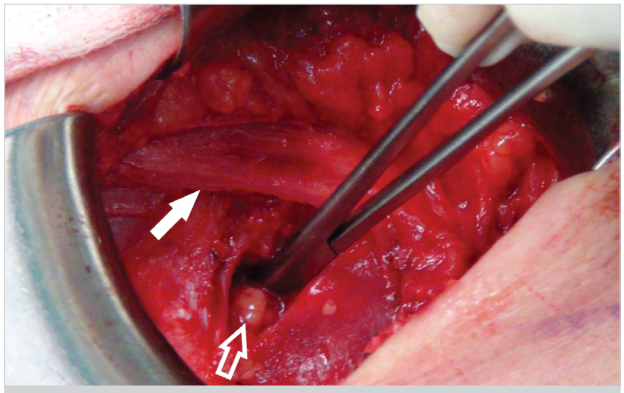

Figure 2. Lumbar hernia, perioperative image after invagination of the herniated mass Full white arrow: Latissimus dorsi muscle; empty white arrow: herniated area

Lumbar hernias are rare lesions that are usually observed after trauma or surgery. Petit's hernia occurs more often in the left side and in males (3, 4). In the present case, the patient was male and had a history of lumbar surgery and left-sided hernia.

There are about 300 reports in the literature; almost all reports are case reports. A general surgeon will have experienced at least a single instance of one or a few lumbar hernias in his/her career (5, 6). Symptoms and presentation of lumbar hernias can vary. They are frequently asymptomatic or may cause back pain in the sciatic nerve distribution area with or without a palpable mass. According to Light, it is the most probable diagnosis in young women and athletes with back pain (7). In differential diagnoses, abscess, hematoma, lipoma, renal tumors, or muscle spasm should be considered. For imaging purposes, CT is accepted as a routine diagnostic technique to evaluate patients with lumbar hernia (3, 5). In the present case, CT revealed herniation of the mass at left lumbar spaces, verified the diagnosis, and guided the surgery.

Natural evaluation of these hernias is a steady growth in size. Surgical treatment is suggested for all lumbar hernias if allowed by the patient's general condition. Several surgical techniques, including simple closure, myoplasties, and plasties using meshes, have been identified as treatment modalities. The laparoscopic approach may be used for small and moderate hernias (3, 8). Although various methods have been defined in the surgical treatment of lumbar hernias, no method has been recommended as the most favorable surgical technique because of the risk of recurrence.

CONCLUSION

Lumbar hernias are rare clinical entities and need suspicion to be diagnosed. Imaging studies, particularly CT, are useful in defining the anatomy and contents. Reconstruction can be achieved with synthetic mesh repair; this can be accomplished by either open or endoscopic methods with minor complications.

Informed Consent: Written informed consent was not obtained due to retrospective nature of the case.

Peer-review: Externally peer-reviewed.

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Case Report

Foreign body in the stomach: Dentures

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ABSTRACT

Although it is mostly observed in childhood, swallowing foreign bodies causes morbidity and mortality of a high percentage in the adult age group. Swallowed foreign bodies can be both harmless as well as life-threatening. The number, shape, size, and time of the swallowed foreign body to get deposited in the specific location determines the type of treatment. Late diagnosis and treatment is an important problem that causes perforation and obstruction. In this article, we presented a 39-year-old male patient who swallowed his denture while sleeping.

Keywords: Surgery, stomach, foreign body, endoscopy

INTRODUCTION

The treatment approach to a swallowed foreign body depends on the size, number, time from swallowing to its deposition in the specific location, and whether the edges are sharp or smooth (1). They are mostly lodged in the esophagus and then the stomach. While most swallowed foreign bodies are removed spontaneously without any need for surgery, some cases are occasionally encountered that require surgical intervention (2). The approaches to be applied are endoscopy, observation, and surgery. For patients presenting in the early stage with the foreign body in the stomach, it can be removed endoscopically in a majority of cases. In delayed cases or those where endoscopic removal cannot be applied, conservative observation is then applied (3). When there is even one complication such as perforation, bleeding, or mechanical intestinal obstruction, a surgical approach is inevitable. In this paper, a patient is presented who swallowed a prosthetic tooth and required surgery.

CASE PRESENTATION

A 39-year-old male patient presented at the Department of Emergency after having swallowed a prosthetic tooth while sleeping. His vital signs were stable. In the physical examination, pulmonary sounds were normal and the intestinal sounds were normo-active. In the abdominal examination, tenderness, defense, or rebound were not determined. The laboratory values were within normal limits. On the pulmonary radiograph, no free air was determined in the mediastinum. On the upright direct abdominal radiograph, the prosthetic tooth was observed as a metal body with opacity (Figure 1). Endoscopy was applied to the patient. The prosthetic tooth was observed in the stomach and was removed as far as the proximal esophagus with endoscopy (Figure 2). The sharp metal parts of the tooth were lodged in the cricopharyngeal narrowness. Because there was a risk of perforation, the procedure was terminated and the tooth was left in the stomach. It was decided to apply laparotomy to prevent the development of any complication. With gastrotomy, the prosthetic tooth of 5×4 cm with sharp metal notches, together with a part of the gum where it was implanted, was removed (Figure 3). No complications developed in the postoperative period and the patient was discharged on the fifth day.

DISCUSSION

The swallowing of a foreign body is a frequent reason for presentation at the emergency department. Although it is less common in adults than children, it is often encountered in those with mental retardation, psychiatric disorders, and drug addiction and in prisoners (4). The foreign bodies swallowed are different according to the age group. In children, they are primarily coins, toys, and pens. In adults, meat, fish, and meat bones; pins; and teeth are the most common foreign bodies. In those with psychiatric disorders and prisoners, belts, razor blades, knives, and stones are the foreign bodies that have been reported to be swallowed (5).

There are three main treatment pathways: endoscopy, observation, and surgery. The majority of foreign bodies are spontaneously passed out of the body with feces without any complications. Studies in the literature have reported spontaneous removal of 75.6% of the foreign bodies, endoscopic removal in 19%, and by a surgical approach in 4.8% (6).

When the patient presents early symptoms and the swallowed foreign body is proven to be in the stomach, endoscopy should be attempted first. If endoscopy is not possible and the foreign body is small or

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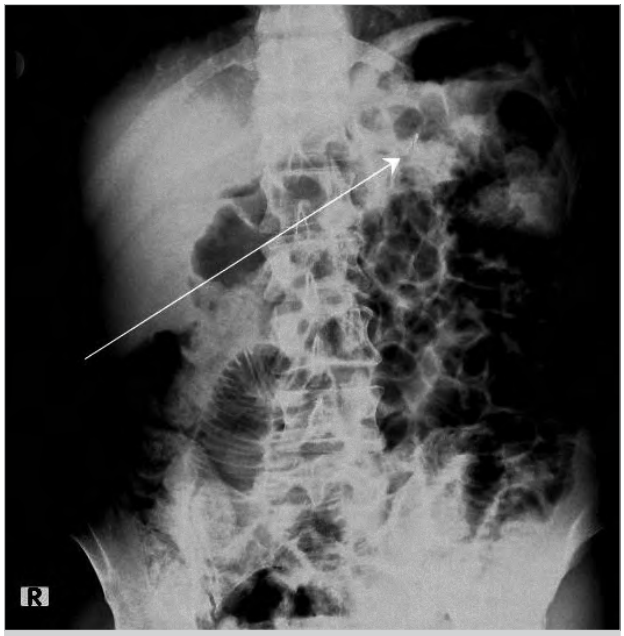

Figure 1. The prosthetic tooth observed as a metal body with opacity on the upright direct abdominal radiograph

Figure 2. The prosthetic tooth in the proximal esophagus

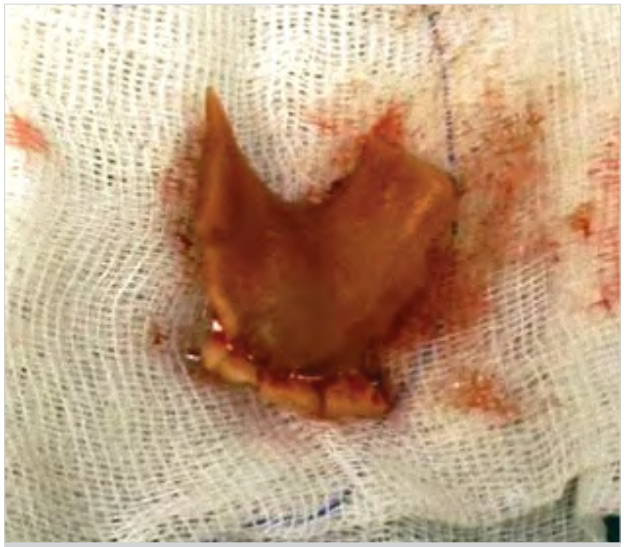

Figure 3. The prosthetic tooth together with palate tissue where it was implanted

has passed into the small intestine, the patient should be kept under observation (7). When there is no movement of sharp or pointed objects (4 cm in length and 2 cm in diameter) for 3 days and of blunt objects for more than 7 days in the gastric or duodenal region, removal by endoscopic or surgical means is required (8). In the current case, endoscopy was initially attempted, but because of the risk of perforation, surgical intervention was required.

CONCLUSION

In the early stages, foreign bodies in the stomach and esophagus can be removed by endoscopy. Because of the low morbidity and mortality and ease of the procedure, endoscopy continues to be the most reliable method. However, foreign bodies that cannot be removed by endoscopy or that create a risk of complications must be removed by a surgical procedure.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Laparoscopic resection for Meckel's diverticulum causing intestinal obstruction

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ABSTRACT

Meckel's diverticulum (MD) is the most common congenital anomaly of the gastrointestinal system with an estimated incidence of approximately 2% of the population. Although most cases are asymptomatic, it has the potential to create complications, such as hemorrhage, inflammation, intestinal obstruction, perforation, and intussusception. Meckel's diverticulum is generally diagnosed incidentally or upon investigation of unexplained gastrointestinal bleeding, perforation, inflammation, or obstruction for both pediatric and adult patients. Complications are often present as surgical emergencies and require resection of the diseased intestinal segment. In doubtful cases, laparoscopy should be the surgical method for both diagnosing and treating MD. Here we present a case of MD causing intestinal obstruction and that was treated by laparoscopic resection.

Keywords: Meckel's diverticulum, laparoscopy, intestinal obstruction

INTRODUCTION

Meckel's diverticulum (MD) is a true diverticulum derived from a persistent vitellointestinal duct and was first described by Johann Meckel in 1812 (1, 2). Meckel's diverticulum occurs on the antimesenteric border of the ileum and in the majority of cases, within 90 cm from the ileoceacal valve. Most cases are asymptomatic with an overall lifetime risk of complications reported at approximately 6.4% (3). Bleeding is the most common presentation in children, representing 50% of MD-related complications among patients younger than 18 years. Intestinal obstruction is the most common presentation in adults with Meckel's diverticula. Diverticulitis, present in 20% of patients with symptomatic Meckel's diverticula, is associated with a clinical syndrome that is indistinguishable from acute appendicitis (4). Although complications due to MD are rare, they often present as surgical emergencies (5). These complications often warrant surgical resection of the diseased segment. Meckel's diverticulum is generally diagnosed incidentally or upon investigation of unexplained gastrointestinal bleeding, perforation, inflammation, or obstruction for both pediatric and adult patients. Here we present a case of MD causing intestinal obstruction and that was treated by laparoscopic resection.

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CASE PRESENTATION

A 24-year old man with no significant medical history and no prior surgical history presented with complaints of abdominal pain, nausea, and vomiting to our emergency unit. The laboratory examination revealed mild leukocytosis (white blood cell count, 13.700). The plain abdominal radiograph revealed dilated small bowel loops with multiple air-fluid levels showing an intestinal obstruction. On physical examination, there was a mild abdominal distention particularly in the upper quadrants of the abdomen with no signs of abdominal rebound tenderness. Abdominal contrast enhanced computed tomography revealed diffuse wall thickness of distal intestinal segments and proximally dilated intestinal segments (Figure 1). Because of the patient's age and clinical history of having no previous surgical history, the preoperative diagnosis was Crohn's intestinal involvement or gastrointestinal lymphoma. Instead of an open surgical procedure, we decided to perform a diagnostic laparoscopy, and an informed written consent was obtained from the patient.

Laparoscopic exploration was performed through a three-trocar operative technique (using a 10-mm optical trocar at the infra-umbilical region; a 5-mm operating trocar at the supra-pubic region, which was changed to a 12-mm trocar during stapling; and a 5-mm operative trocar at the right lower quadrant on McBurney's point) with an angled (30°) laparoscope. Entrance to the abdomen was achieved by an open technique. First, the ileocecal valve was found, and an exploration was conducted through the proximal intestinal segments. At the exploration, a w-shaped intestinal obstruction was observed approximately 100 cm proximal to the ileocecal valve. After blunt dissection of the intestine, an inflamed MD was found to be the reason of the intestinal obstruction (Figure 2). The vascular pedicle of the resected intestinal segment was ligated using Ligasure™ (Covidien, Colorado, USA). The resection of MD was performed using 60 mm Endo GIA™ (Blue, 3.5 mm, Covidien, Colorado, USA) with additional reinforcement (Figure 3). The pathological specimen was extracted from the suprapubic port incision in an endoscopic bag. A drain was placed at the rectovesical fossa, and the operation was terminated. There was no more

Figure 1. Axial contrast-enhanced arterial images of the abdominal computed tomography scan; diffuse wall thickness of distal intestinal segments (white arrow) and dilatation of the proximal intestinal segments (gray arrow)

than 100 mL bleeding during the operation. The operation duration was 78 min overall. Finding the obstructive intestinal segment in a distended abdomen was the hard part of the operation. The operation was performed in the Trendelenburg position to achieve an easier exploration and resection. The postoperative course was uneventful, and the patient was discharged on the third postoperative day.

DISCUSSION

Meckel's diverticulum is a congenital, intestinal blind pouch that results from an incomplete obliteration of the vitelline duct during the fifth week of gestation. It is a true diverticulum that usually arises from the antimesenteric border of the distal part of the ileum and contains all layers of the normal intestinal wall. Although it generally remains silent, life-threatening complications may arise, making it important to have a detailed knowledge of its anatomical and pathophysiological structure and properties to deal with such complications (6). Meckel's diverticulum is extremely difficult to diagnose both clinically and radiologically as the symptoms and imaging features are nonspecific. Hemorrhage is the most frequent complication of the condition in the pediatric population and arises secondary to ulcerations caused by acid secretion from the ectopic mucosa. Obstruction because of intussusception or adhesions, ulceration, and inflammation (diverticulitis) occur more frequently among adults (7). Complications appear more frequently among males, with a reported 3–4 times greater incidence in males.

Cullen et al. (3) studied the outcomes of surgical management of MD-related complications and determined that the operative mortality and morbidity rates were 2% and 12%, respectively, and that the cumulative risk of long-term postoperative complications was 7%; in contrast, the analysis of patients receiving incidental diverticulectomy showed that the operative mortality, morbidity, and risk of long-term postoperative complications were lower (1%, 2%, and 2%, respectively). It is generally recommended that MD discovered incidentally during operation should be removed, regardless of the patient's age.

Sasikumar et al. (8) reported a case of small bowel obstruction due to the torsion of gangrenous MD, and they performed

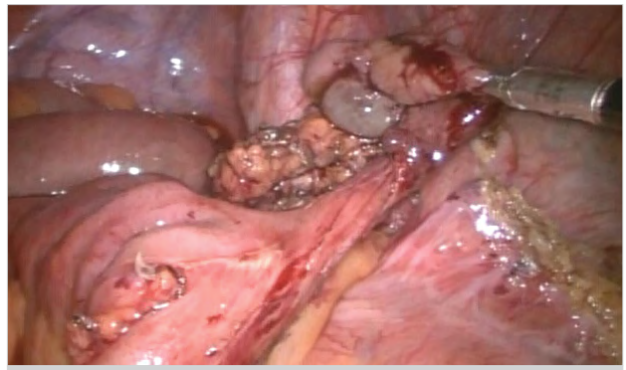

Figure 2. Intraoperative image of the inflamed Meckel's diverticulum

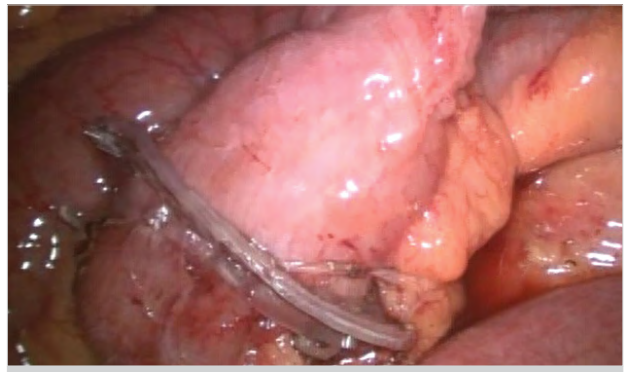

Figure 3. Image of the intestine after the laparoscopic resection of Meckel's diverticulum

resection and anastomosis by an open approach. Ding et al. (9) reported the role of laparoscopy on the surgical treatment of perforated MD, and they found it to be safe and effective for diagnosis and the therapeutic role. Alemayehu et al. (10) reported a retrospective analysis of laparoscopically treated complicated MD in patients. Eight of these patients had intestinal obstruction and were laparoscopically treated without complication.

The preoperative diagnosis of MD is usually difficult because of its various clinical presentations. Most of the cases are misdiagnosed as acute appendicitis. Incidentally diagnosed MD and complicated MD require a surgical intervention. Usually, McBurney's point or an inferior umbilical median incision is used for laparotomy, and an open approach is used in the treatment of MD.

CONCLUSION

In patients with doubtful diagnosis, as in our case, laparoscopy is a feasible, safe, and effective surgical method for diagnosing MD, and it also helps treat the condition.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.K., İ.Ö.; Data Collection and/or Processing - İ.Ö., Ö.L.; Analysis and/or Interpretation - Ö.Y.; Literature Review - E.Ş., Ö.Y.; Writer - Ö.Y.; Critical Review - Ü.A.

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Case Report

A rare case: Retrocecal appendicitis adherent to the liver capsule

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ABSTRACT

The cases of appendicitis take an important place in the hospital emergency departments and it must be kept in mind in the differential diagnosis of patients presenting with abdominal pain. Related to cecum, the appendix can be found in many different positions; however, it is mostly observed descending intraperitoneally (31–74%) and at the retrocecal region (26–65%). In this case report, we present the case of a 26-year-old female patient admitted to the emergency room with a colic pain in the right upper quadrant for about 2 days. Computed tomography revealed contamination in the fatty plans around the cecum and adhesive retrocecal appendicitis from the liver to the retroperitoneum. Appendectomy was performed. The pathology result was gangrenous appendicitis. In the literature, there is no similar case of appendicitis with hepatic adhesions. In conclusion, we want to emphasize that physicians and surgeons in the emergency departments must be more careful during the differential diagnosis of a patient with appendicitis and atypical symptoms and a more detailed investigation is required.

Keywords: Appendicitis, retrocecal appendix, liver capsule

INTRODUCTION

Appendicitis cases play an important role in hospital emergencies and should be considered in the differential diagnosis of patients with abdominal pain (1). If the appendicitis cannot be diagnosed and the patients leave the hospital with another diagnosis, clinical complications such as appendix perforation or plastron state of intra-abdominal abscess can develop (2). The cecum appendix can be found in many different positions, particularly descending intraperitoneally (31–74%) and at the retrocecal region (26–65%). According to the location of the appendix, patients can be admitted with a different history and physical examination findings can also be different. One of them is an infection in the retrocecal appendix (3). Retrocecal appendicitis may present with different clinical symptoms. Due to the location of the retrocecal appendix, right lower quadrant tenderness may not be observed. Therefore, there could be difficulties in the diagnosis (4).

In half of the retrocecal appendicitis cases, atypical clinical symptoms can be observed (5). In this case, the appendix was in the retrocecal region and physical examination was obviously positive in the right upper quadrant. Right upper quadrant pain can rule out the diagnosis of appendicitis, and mostly suggests cholecystitis, gastritis, duodenal ulcer, and other liver or gallbladder pathologies; therefore, we wanted to present this unusual case in detail. In retrocecal appendicitis cases, the pararenal abscess can be observed added to the appendicitis or infection can also spread to the right paracolic space, right subphrenic, and subhepatic area (6, 7). If our case had a diagnosis other than appendicitis, in the following days, a retroperitoneal abscess could have occurred.

There is no similar case report to ours in the literature and we wanted to highlight that appendicitis cases can present with different clinical symptoms and during the differential diagnosis of patients presenting with abdominal pain, it should be kept in mind.

CASE PRESENTATION

A 26-year-old female patient admitted to the emergency room with a colic pain in the right upper quadrant for about 2 days. In her history, there were only two pregnancies and two live births.

Vital parameters were as follows; blood pressure (BP): 110/70 mm-Hg, pulse: 86/min fever: 37.8°C.

In the physical examination; bowel sounds were normoactive with auscultation; there was tenderness in all abdominal regions and rebound in the right upper quadrant. No other findings were observed in the other systems. Acute cholecystitis was first diagnosed; blood tests and ultrasound (USG) were performed.

The results of the blood tests were as follows: WBC: 15800/mm^3, Hgb: 13.6 g/dL, hematocrit: 39.8%, urea 11 mg/dL Cr: 0.64 mg/dL, AST: 12 IU/L, ALT: 12 IU/L, total bilirubin: 0.5 mg/dL, direct bilirubin: 0.3 mg/dL.

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USG showed normal gallbladder wall thickness and no calculi and no calculi or hydronephrosis in the kidneys.

Thus, the diagnosis of acute cholecystitis was excluded. In order to investigate the cause of pain in the abdomen, computed tomography (CT) was requested. CT revealed contamination in the fatty plans around the cecum and adhesive retrocecal appendicitis from the liver to the retroperitoneum. Contamination was also observed in the adipose tissue under the liver (Figure 1, 2).

After the general surgery consultation with the diagnosis of acute abdomen, the patient underwent surgery immediately. Appendectomy was performed with the right paramedian incision. The stump was buried and mesoplasty was performed. No other pathology was found in the abdomen. It was phlegmonous from the tip of the appendix and joined through retroperitoneum to the liver capsule (Figure 3). The pathology result revealed gangrenous appendicitis. Postoperatively, IV antibiotics and analgesics were started. She was mobilized the first day. She was discharged due to her well-being.

Figure 1. There is contamination in the fatty plans around the cecum

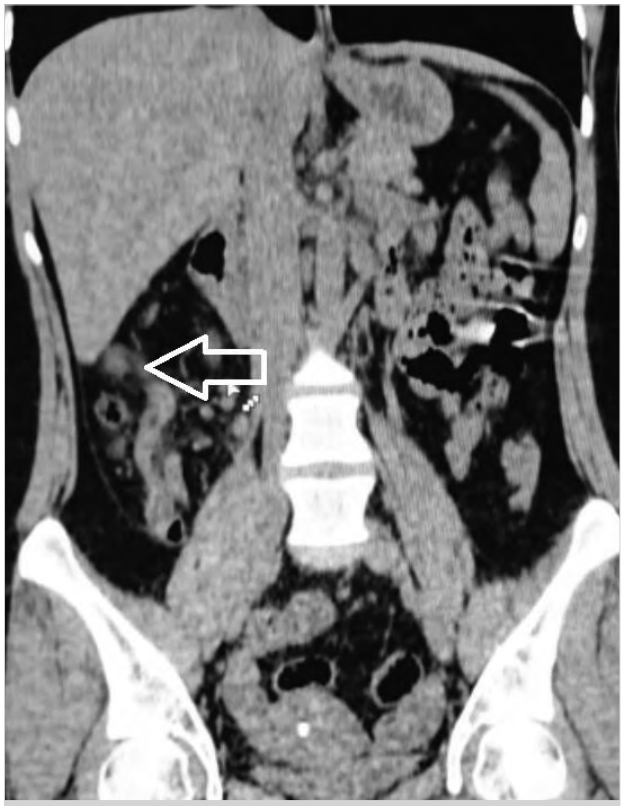

Figure 2. Appendix tissue extension into the liver

A signed written informed consent was taken from the patient.

DISCUSSION

Despite improvement in the techniques, the diagnosis of acute appendicitis remains challenging and the complications of the disease and the rate of negative laparotomy have not been reduced significantly (8). Complaints and symptoms may be atypical in patients with retrocecal appendicitis and can imitate right upper quadrant and right flank pathologies such as acute cholecystitis, renal colic, and diverticulitis (9). The location of the appendix can vary according to the position and shape of the cecum in organogenesis. The incidence of retrocecal appendix is 26–65% (10).

In this case, there was obviously tenderness, rebound, and defense in the right upper quadrant on physical examination. Moreover, she had anorexia and sometimes nausea complaints in the last 2 days. In appendicitis, generally pain starts from the epigastric area; anorexia symptoms and the right lower quadrant pain occur in the next few days. Therefore, this case is atypical. Routine USG is used in the diagnosis as the first step. A study on children's cases showed that the appendicitis diagnosis rate is 99% in suspected cases (11). Another study showed that the use of USG in the suspected cases diminished the negative laparotomies and the morbidity rate because of a delay in diagnosis (12).

However, in adults, it is indicated that non-contrast CT is superior to USG and CT decreases the false laparotomy rates (13). When clinically, gallbladder, hepatobiliary, or urinary tract pathologies are suspected in patients in the emergency departments, USG is frequently performed. With this in

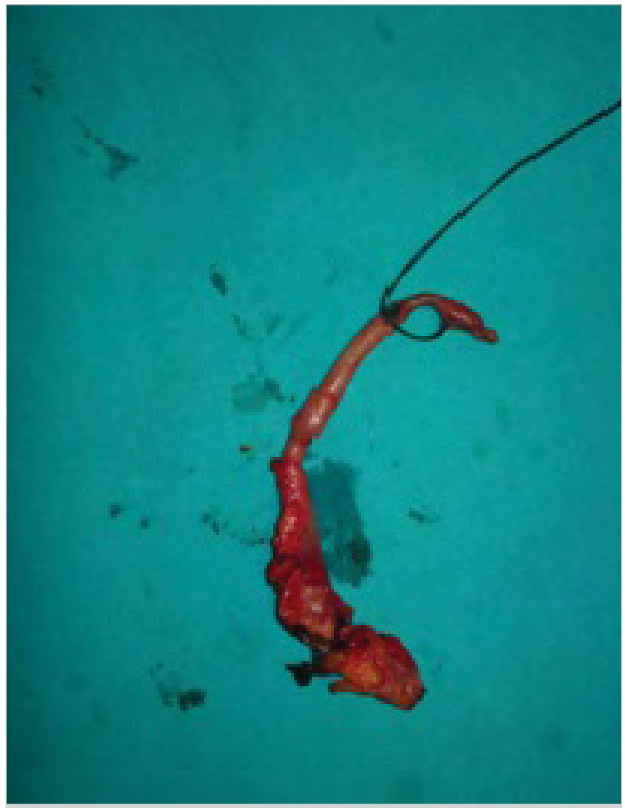

Figure 3. The phlegmonous end portion of the appendix tissue

mind, liver abscess and fluid collection in the subhepatic or the right flank region can be observed on ultrasonography in retrocecal appendicitis cases (11). However, in this case, no pathology was detected on USG and the diagnosis was confirmed by CT.

In the inflammatory process of retrocecal appendix, it can spread to the perirenal, adrenal, and subhepatic region (6). In our case, the appendix was attached to the liver tissue. In the literature, no cases of appendicitis with hepatic adhesions have been reported.

In this case, the cause of the right upper quadrant pain (presence of Murphy's sign) was the irritation of the liver fascia. Here we would like to emphasize again that further research should be performed by the physicians and surgeons in emergency rooms for the differential diagnosis of patients admitting with atypical symptoms. With wrong diagnosis and treatment, the patient's symptoms can become more complicated in the coming days and this can increase morbidity and mortality. We recommend that the use of additional imaging systems for the possible diagnoses without hesitation in patients with atypical signs is important. We first observed USG in our case and although we could not find any pathology, we required a non-contrast abdominal CT for the differential diagnosis. After CT, we were able to properly diagnose.

CONCLUSION

When acute appendicitis is not suspected clinically in patients with abdominal pain in the emergency departments; we need to remember that the physical examination findings can differ according to the localization of the appendix. As observed in this case, one can be faced with retrocecal appendicitis attached to the liver capsule. Furthermore, it should be kept in mind that retrocecal appendicitis can be complicated and an abscess can occur in the abdomen.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.B.; Design - H.B., Z.T.Ö.; Supervision - M.S., S.K.; Funding - H.B., Z.T.Ö.; Materials - H.B.; Data Collection and/or Processing - H.B., S.K., M.S., M.F.E.; Analysis and/or Interpretation - H.B., M.S., M.F.E.; Literature Review - H.B., Z.T.Ö.; Writer - H.B., Z.T.Ö.; Critical Review - M.S., M.F.E.; Other - S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Closed-perforation of gastric fundus and gastric outlet obstruction caused by a giant gastric trichobezoar: A case report

Bünyamin Gürbulak[1], Özgür Seğmen[1], Taşkın Rakıcı[2], Kenan Büyükaşık[1], Mazlum Yavaş[1]

ABSTRACT

A bezoar is a mass formed because of the accumulation of indigestible material in the stomach and/or small intestine. Bezoars are rare but occasionally occur with acute abdomen findings. Bezoars form as a result of changes in the gastrointestinal system anatomy and physiology and repetitive exposure to the ingested material. These materials can include vegetables with high fiber content (phytobezoars), non-animal origin fats, hair (trichobezoars), or drugs such as anti-acids (pharmobezoars). Gastric bezoars frequently occur after gastric surgery. Psychiatric disorders such as trichotillomania (an irresistible urge to remove and swallow one's own hair) are frequently the underlying reason in patients without a history of gastric surgery. In this article, we presented a giant gastric trichobezoar obstructing outlet and causing closed-perforation and abscess formation of gastric fundus in a 30-year-old woman.

Keywords: Bezoar, trichobezoar, closed-perforation of stomach, gastric outlet obstruction

INTRODUCTION

Bezoars are masses comprising of non-digested and/or partially digested food debris or foreign particles accumulating in the stomach or the small intestine. Bezoars usually develop in the stomach or the small intestine; however, bezoar formation in the colon is rare. These masses can be classified as bezoars that are formed because of a high-fiber diet (phytobezoars), indigestible materials such as hair, fingernails, and animal fat (trichobezoars) or accumulation of anti-acids or anti-hypertensive drugs (pharmacobezoars). The most common form in clinical practice is phytobezoars (1).

Stomach bezoars usually develop following gastric surgery. Diabetes mellitus, high fiber diet, insufficient chewing function, dental pathologies, myotonic muscular dystrophy, or cimetidine treatment may rarely be the cause. Among those patients without a history of gastric surgery, the most common underlying pathology is psychiatric disorders such as trichotillomania (1, 2).

Bezoars may be clinically asymptomatic or present with chronic abdominal pain, dyspepsia, gastric ulcers, gastrointestinal hemorrhage, perforation due to pressure necrosis, intestinal intussusception, and ileus. Adult mortality rates of up to 30% related to gastrointestinal bezoars have been reported (3).

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Our aim in this paper is to present a case of giant gastric trichobezoar treated with emergency surgical intervention, thereby stressing the importance of clinical doubt for correct diagnosis before complications arise because bezoars can be asymptomatic or present with nonspecific symptoms.

CASE PRESENTATION

A 30-year-old female patient, five days after premature birth and while under follow-up in the Obstetrics and Gynecology Clinic was checked for the need for surgery due to abdominal pain, nausea, and hematemesis. The vital signs were stable and within the normal limits. The body temperature was 37.2°C. There was mild abdominal distention with epigastric tenderness and guarding. The laboratory findings were normal except for a white blood cell count of 13200/mm^3 and a CRP finding of 95 mg/L. Abdominal computerized tomography (CT) showed presplenic abscess formation and a giant intragastric mass totally occluding the stomach (Figure 1, 2). Detailed patient history revealed a long history of trichophagia and trichotillomania. Emergency surgical intervention was planned with the prediagnosis of complicated gastric bezoar. Laparotomy revealed a mass formation at the gastric fundus having caused closed perforation. When the abscess was drained after exploring the perforation site through sharp and blunt dissection; trichobezoar filling the entire stomach could be observed (Figure 3). The giant trichobezoar mass was removed from the stomach through an anterior gastrotomy, which extended longitudinally from the site of perforation at the fundus. Pressure ulcers at the gastric antrum and the angular notch could also be observed through the gastrotomy. After the debridement of the borders of the perforation, the gastrotomy incision was repaired using double sutures. On inspection, the bezoar mass was a hairball with a smooth surface having taken the shape of the stomach and the hair strands could only be removed by tearing (Figure 4). Oral feeding was started on the postoperative fifth day. The patient was referred to a psychia-

trist. Depressive behavioral disorder was diagnosed accompanying trichophagia and treatment was planned. The patient was discharged from the hospital on postoperative day 10 with no complications.

DISCUSSION

Bezoars are masses of non-digested food particles and fibrous materials in the gastrointestinal system (GIS). They can be found anywhere in GIS, although they most frequently form in the stomach and the small intestine (3, 4).

Among bezoars, phytobezoars are the most common and the best known group. Phytobezoars are reported to be developing in up to 70% of adults having undergone gastric surgery (3). The main cause in the pathophysiology of bezoars after gastric surgery is large masses of food rapidly passing to the duodenum before being digested because of decreased acid-pepsin secretion or pyloric dysfunction. Diabetic gastroparesis, pathologies such as chronic gastritis causing decreased gastric acidity and mucus secretion, and the resulting impairment of digestion and motility are other major causes of phytobezoar formation (4). Phytobezoars can also form in patients with chewing dysfunction or dental problems because of excess consumption of high fiber food such as citrus fruits, fresh beans, fig, and fruit seeds (5). For patients without a history of abdominal surgery, phytobezoars are responsible for less than 2% of the cases of small intestinal obstruction (6).

Trichobezoars are formed by oral ingestion of mostly human hair and rarely animal fur and/or wool and filaments from furniture (6). However, the mechanism for the formation of trichobezoars is obscure. According to the most popular hypothesis, bezoars originate from strands of hair in the gastric folds combining with mucus and food particles and growing in size. However, this hypothesis fails to explain why hair strands hold on to the stomach in the first place (7). Trichobezoars are usually found in young female patients with mental retardation and/or psychiatric disorders such as trichotillomania or trichophagia. Trichobezoars are usually accompanied by psychiatric disorders such as obsessive compulsive personality disorder, pica, anorexia nervosa, or as in our case, depressive behavioral disorder.

Gastrointestinal system bezoars can be asymptomatic and incidentally diagnosed as well as presenting with gastrointestinal hemorrhage, ulcers, perforation, or intestinal obstruction (8). Stomach bezoars can cause nonspecific symptoms such as epigastric tenderness and dyspepsia or result in nausea and vomiting because of gastric outlet obstruction or abscess formation because of closed perforation.

Because the treatment of complicated GIS bezoars includes surgical intervention, a correct preoperative diagnosis of bezoar is essential, which itself requires clinical doubt. In addition to detailed patient history and careful physical examination, upper GIS endoscopy and radiological tests such as abdominal X-ray, ultrasound, or abdominal CT are helpful in diagnosis. Among these methods, upper GIS endoscopy and abdominal CT with contrast are the most reliable diagnostic tools (9). Upper GIS endoscopy is especially useful in determining the type of bezoar in cases with gastric bezoars. In addition to its diagnostic use, endoscopy has been used therapeutically in the management of bezoars. Endoscopic treatment options involving the removal of gastric trichobezoars after crumbling them by baskets, snare, and lithotripter forceps have been unsuccessful (10). Phytobezoars, on the other hand, can be treated medically with motility stimulating, enzymatic, pro-kinetic, and mucolytic agents as well as endoscopically by fragmenting them with snares and forceps.

Figure 1. A giant mass that fills the lumen of the stomach with abscess formation between the stomach and spleen

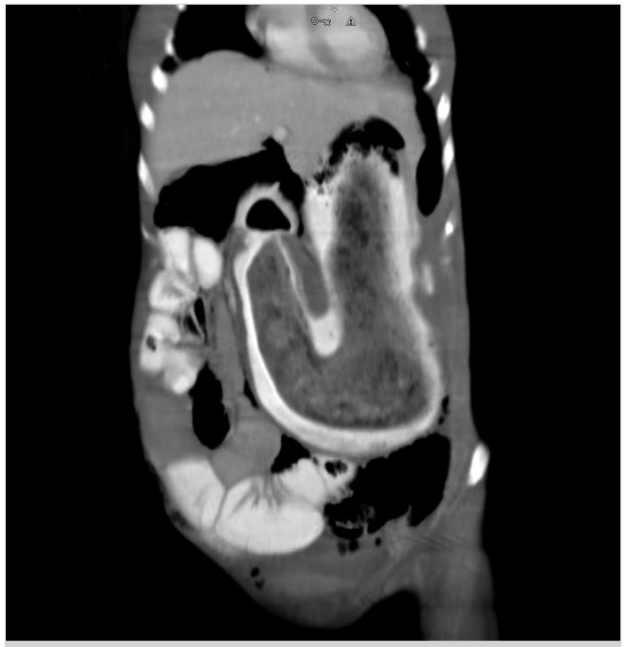

Figure 2. Computerized tomography appearance in the sagittal sections of the giant mass that fills the stomach lumen

In abdominal CT scans, bezoars appear in GIS as well demarcated, oval masses with air bubbles in them. According to the localization of the bezoar mass in the GIS lumen, proximal segments are dilated and distal segments in normal caliber (9).

For our patient who was evaluated for abdominal pain, nausea, and hematemesis, intragastric mass in the abdominal CT and a history of trichophagia were alerting signs for gastric trichobezoar. Because of the abscess pouch in the CT scan near the fundus, in front of the spleen, and having air fluid levels suggesting a closed perforation, a decision for emergency surgical intervention without prior endoscopy was made.

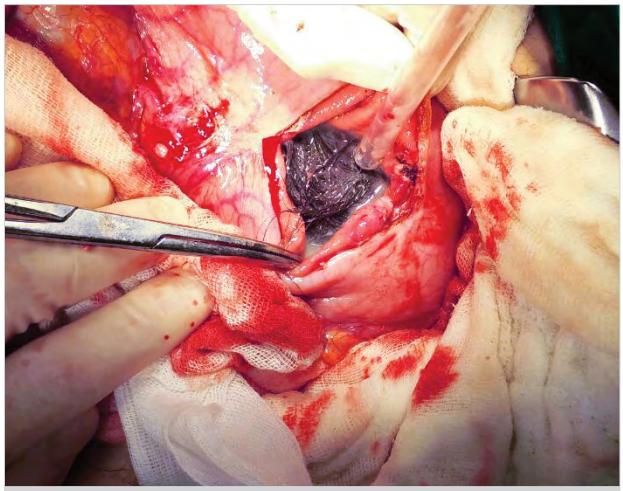

Figure 3. The trichobezoar in the gastric lumen reached via anterior gastrostomy

Figure 4. The giant trichobezoar in the shape of the stomach

CONCLUSION

Gastrointestinal bezoars can be silent until they become complicated and symptomatic. In patients with chronic abdominal pain with no signs of malignancy in laboratory and radiological tests, medical history should be elaborated and for those with a positive history of psychiatric disorders or trichophagia, bezoar should be suspected.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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Author Contributions: Concept - B.G.; Design - B.G., K.B.; Supervision - B.G., Ö.S.; Funding - B.G., Ö.S., T.R.; Materials - B.G.; Data Collection and/or Processing - B.G., Ö.S., M.Y.; Analysis and/or Interpretation - B.G., Ö.S., T.R., K.B., M.Y.; Literature Review - B.G., Ö.B., T.R., K.B., M.Y.; Writer - B.G., Ö.S.; Critical Review - B.G., Ö.S., T.R., K.B., M.Y.; Other - B.G., Ö.S., T.R.

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