ISSN 2564-6850
E-ISSN 2564-7032

TURKISH JOURNAL OF SURGERY

VOL. 34 | ISSUE 2
JUNE 2018

AVES

turkjsurg.com

TURKISH JOURNAL OF SURGERY

Türk Cerrahi Derneği adına sahibi / Owner on behalf of the Turkish Surgical Association: Salim Çağatay Çifter • Sorumlu Yazı İşleri Müdürü / Responsible Manager: Mustafa Şahin • Yayın türü / Publication Type: Yerel süreli / Local periodical • Basım yeri / Printed at: Matsis Matbaa Hizmetleri San. ve Tic.Ltd. Şti, Tevfikbey Mah., Dr. Ali Demir Cad. No: 51, 34290 Sefaköy, Turkey (+90-212-624 21 11) • Basım tarihi / Printing Date: Haziran 2018 / June 2018 • Türk Cerrahi Derneği tarafından yayınlanmaktadır / Published by Turkish Surgical Association, Koru Mah. Ihlamur Cad. No:26 Çayyolu-Çankaya, Ankara, Turkey +90 (312) 241 99 90

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Aims and Scope

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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Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.turkjsurg.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Turkish Surgical Association.

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- 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).

Manuscript Types

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.

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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: 709-711.

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.

REVISIONS

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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Publisher: AVES
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TURKISH JOURNAL OF SURGERY

Contents

Review

83 | Comments on the new groin hernia guidelines: What has changed? What has remained unanswered?
Hakan Kulaçoğlu; Ankara, Turkey

Original Investigations

89 | Surgical approaches for papillary microcarcinomas: Turkey's perspective
Özer Makay, Murat Özdemir, Yasemin Giles Şenyürek, Fatih Tunca, Mete Düren, Mehmet Uludağ, Mehmet Hacıyanlı, Gökhan Içöz, Adnan Işgör, Serdar Özbaş, Zehra Özcan, Serdar Tezelman; İzmir, İstanbul, Ankara, Antalya, Turkey

94 | Effects of body mass index on cecal intubation time in women
Banu Karapolat, Üzer Küçüktülü; Trabzon, Turkey

97 | Importance of informed consent defined by General Surgery Associations in Turkey
Erdinç Kamer, Ali Rıza Tümer, Turan Acar, Burak Uyar, Gülden Ballı, Fevzi Cengiz, Mesut Özoğul, Mehmet Hacıyanlı; İzmir, Ankara, Antalya, Turkey

101 | Self-expandable metallic stent application for the management of upper gastrointestinal tract disease
Arif Emre, Mehmet Sertkaya, Sami Akbulut, Ozan Erbil, Nursel Yurttutan, İlhami Taner Kale, Ertan Bülbüloğlu; Kahramanmaraş, Malatya, İzmit, Turkey

106 | Splenectomy proportions are still high in low-grade traumatic splenic injury
Ahmet Korkut Belli, Önder Özcan, Funda Dinç Elibol, Cenk Yazkan, Cem Dönmez, Ethem Acar, Okay Nazlı; Muğla, Turkey

111 | Effect of sildenafil citrate on the liver structure and function in obstructive jaundice: An experimental study
Tamer Şimşek, Ömer Faik Ersoy, Zeki Özsoy, Erdinç Yenidoğan, Hüseyin Ayhan Kayaoğlu, Namık Özkan, Mustafa Şahin; Tokat, Turkey

117 | Management of huge and extraordinary metal-penetrating injuries to the hand
Osman Akdağ, Gökçe Yıldıran, Mehtap Karameşe; Konya, Turkey

121 | Approach to the diagnosis and treatment of mesenteric panniculitis from the surgical point of view
Cemal Kaya, Emre Bozkurt, Pınar Yazıcı, Ufuk Oğuz İdiz, Mert Tanal, Mehmet Mihmanlı; İstanbul, Turkey

125 | Survival outcomes after D1 and D2 lymphadenectomy with R0 resection in stage II–III gastric cancer: Longitudinal follow-up in a single center
Adam Uslu, Baha Zengel, Enver İlhan, Ahmet Aykas, Cenk Şimşek, Orhan Üreyen, Ali Duran, Gökalp Okut; İzmir, Turkey

131 | Where do these guests come from? A diagnostic approach for metastatic lymph nodes
Yelda Dere, Sümeyye Ekmekçi, Serkan Çelik, Özgür İlhan Çelik, Özcan Dere, Volkan Karakuş; Muğla, İzmir, Turkey

Case Reports

137 | Missed thyroid gland after total thyroidectomy
Sangar M.faroq Abdulrahman, Serkan Teksöz, Sina Ferahman, Süleyman Demiryas, Yusuf Bükey, Ateş Özyiğin; İstanbul, Turkey

140 | Regression in local recurrence in the contralateral breast following mastectomy in bilateral locally advanced breast cancer: a comparison of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios
Abdullah Durhan, Gamze Durhan, Aydan Eroğlu; Ankara, Turkey

143 | An incidental giant preperitoneal fibrolipoma diagnosed during laparoscopic cholecystectomy
Fatih Başak, Mustafa Hasbahçeci, Tolga Canbak, Metin Yücel, Aylin Acar, Abdullah Şişik, Gürhan Baş, Murat Hakan Karabulut, Gözde Kır; İstanbul, Turkey

TURKISH JOURNAL OF SURGERY

146 | Adrenal angiosarcoma
Gülden Cancan, Serkan Teksöz, Süleyman Demiryas, Murat Özcan, Yusuf Bükey; İstanbul, Turkey

149 | Hyalinizing trabecular tumor of the thyroid gland
Sefa Ergün, Ozan Akıncı, Tülin Öztürk, Adem Karataş; İstanbul, Turkey

152 | Coexistence of gastric multiple neuroendocrine tumors with unusual morphological features and gastric signet-ring cell carcinoma
Nesrin Uğraş, Pınar Sarkut, Ömer Yerci, Ersin Öztürk; Bursa, Turkey

155 | Laparoscopic surgical transmesocolic jejunostomy: A new surgical approach
Alberto Pagan, Alessandro Bianchi, José Antonio Martínez Marina Jiménez, Xavier Francesc Gonzalez; Palma De Mallorca, Spain

158 | Chronic visceral ischemia: An unusual cause of abdominal pain
Turan Acar, Volkan Çakır, Nihan Acar, Kemal Atahan, Mehmet Hacıyanlı; İzmir, Turkey

162 | The patients with Peutz-Jeghers syndrome have a high risk of developing cancer
Cengiz Tavusbay, Turan Acar, Haldun Kar, Kemal Atahan, Erdinç Kamer; İzmir, Turkey

TURKISH JOURNAL OF SURGERY

Editorial

Dear Colleagues,

We feel right proud of presenting the 2nd issue of the 34th volume of the Turkish Surgical Journal to our readers on time. In the journal, a lot of nameless heroes contribute to the process including the acceptance of manuscripts for publication, their assessments, and their being prepared for publication. Once again, I would like to thank all my teammates for their contributions.

The National Surgical Congress was held on April 11-16, 2018. Many colleagues from our country and others attended this congress. As usual, innovations in general surgery were discussed in this congress. Moreover, courses and meetings were organized for solving the problems encountered by our colleagues working in peripheral hospitals.

I thank the President of Congress, Prof. Dr. Orhan KOZAK and his team for their productive congress organization and I congratulate them on behalf of our colleagues.

This issue includes a review, original research articles, and case reports. We pay attention to choose interesting, educative, and innovative studies on almost all areas of general surgery. For our journal to be included among others that are scanned by SCI and SCI Expanded, I would like to request you to submit your valuable studies to our journal and to refer the articles published in our journal in your studies and I present my gratitude for your supports.

Wish you success in your studies.

Prof. Dr. Mustafa ŞAHİN

Editor in Chief

Turk J Surg 2018; 34: 83-88
DOI: 10.5152/turkjsurg.2018.4146

Review

Comments on the new groin hernia guidelines: What has changed? What has remained unanswered?

Hakan Kulaçoğlu

ABSTRACT

Guidelines are meant to evaluate the options available in the current circumstances and suggest the proper solutions for particular problems. The duty of a guideline is to present a basis for decision-making. Surgical options for the treatment of groin hernias are numerous. Recently, a joint guideline called *"International Guidelines for Groin Hernia Management"* was developed by five continental hernia societies, the International Endo hernia Society, and the European Association for Endoscopic Surgery. This article aimed to review the methodology, statements, and recommendations of the new guidelines and emphasized the importance of the tailored surgery for groin hernias. Spreading the guidelines may provide surgeons with an up-to-date knowledge and be useful for better outcomes in groin hernia surgery.

Keywords: Femoral, groin, guidelines, hernia, inguinal, laparoscopy

INTRODUCTION

Dictionary meaning of the word "guidelines" is a set of standards, criteria, or specifications to be used or followed while performing certain tasks (1). In Medical Sciences, guidelines are a series of suggestions that are published by official institutions or associations where independent experts exist for the managements of diseases (2). Guidelines evaluate the available options in the current circumstances and suggest the proper solutions for particular problems. They are not prescriptive or directive, but physicians who do not follow these current guidelines may have to face medico-legal issues. In other words, the responsibility of a guideline is to present a basis for decision-making (3).

The earliest example of guidelines in literature was published by the American Medical Association (AMA) to be followed in human experimentation. Twenty-two years later, the AMA Judicial Council published the Ethical Guidelines for Organ Transplantation (4). To date, there are thousands of guidelines in the archives of U.S. Department of Health and Human Services Agency for Healthcare Research and Quality (5).

Surgical options for the treatment of groin hernias are numerous. Surgeons usually select the technique that they learned from their seniors; they generally display conservatism in their practice (6). In 1993, the Royal College of Surgeons published a clinical guideline for the management of groin hernias in adults (7). Soon after, in 1995, a North American publication claimed that a consensus on hernia repair is unlikely (8). Indeed, the guideline could not initially seem to affect daily practice. There was a wide range of repair techniques and postoperative advice by consultant general surgeons (9). However, the adherence to the guideline began increasing within a decade (10). Progress may be slower in general hospitals where many surgeons works, but specific centers where hernia surgeons are employed may adapt faster (11). The first comprehensive guideline on groin hernia surgery was constituted by the European Hernia Society (EHS) in 2009 (12). Two years later, the International Endo hernia Society (IEHS) created a guideline for laparoscopic/endoscopic treatment of inguinal hernia (13). Both guidelines have raised great interest among surgeons. The EHS guidelines were updated in 2014 (14), whereas the IEHS guidelines were updated in 2015 (15). Very recently, a joint guideline called "*International Guidelines for Groin Hernia Management*" was developed by five continental hernia societies, IEHS, and the European Association for Endoscopic Surgery (16). This article was aimed to review this latest guideline on groin hernia surgery and analyze the differences from the previous ones.

METHODOLOGIES FOR THE HERNIA GUIDELINES

Guidelines in medical practice are mainly based on category or level of the evidences, and they present the strength of recommendations. Systematic reviews and good-quality randomized controlled trials (RCTs) provide the most valuable and reliable sources and create Level 1 evidences and Grade A recommendations, whereas expert opinions create Level 4 and Grade D recommendations (17). Groin hernia guidelines have followed the same pathway.

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Cite this paper as:
Kulaçoğlu H. Comments on the new groin hernia guidelines: What has changed? What has remained unanswered? Turk J Surg 2018; 34: 83-88.

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Received: 28.02.2018
Accepted: 09.03.2018

Table 1. The macro structures of the hernia guidelines

Guidelines	Publication Year	Number of Participant	Number of Chapters	Number of Statements	Number of Recommendations/ Conclusions	Number Pages
EHS	2009	18	18	31	37	61
IEHS	2011	22	14	124	96	71
EHS update	2014	17	-	-	20	13
IEHS update	2015	25	18	37	29	33
International	2018	54	31	132	87	165

EHS: European Hernia Society; IEHS: International Endohernia Society

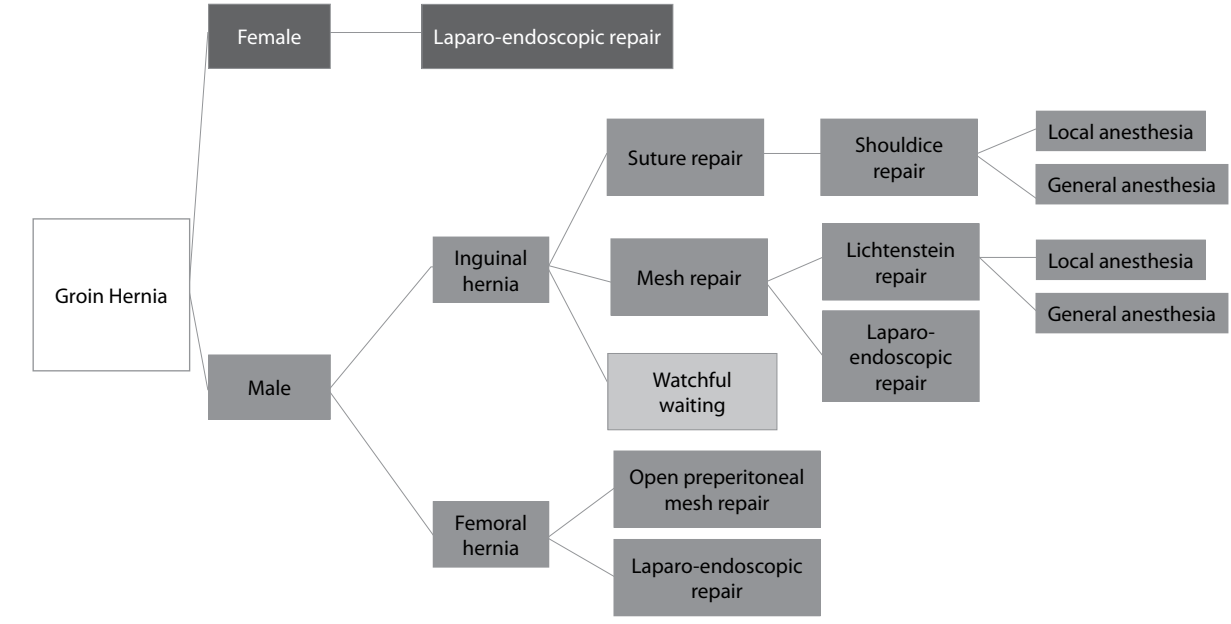

Figure 1. An algorithm for groin hernia management

The EHS guidelines were published in the journal *Hernia* in 2009 (12), whereas the IEHS guidelines were published in the journal *Surgical Endoscopy* in 2011 (13). The EHS guidelines were updated with new Level 1 studies in 2014 with 20 new conclusions (14), whereas the IEHS guidelines were updated in 2015 with 37 statements and 29 conclusions (15).

The new *International Guidelines for Groin Hernia Managements* has been the most comprehensive source in terms of volume (16). These guidelines were published by a group of surgeons named as "*The Hernia Surge Group*." For the first time, there was also an anesthesiologist pain expert. Steering Committee comprised 10 hernia surgeons. There were also 40 other members in the group. In addition, three external reviewers were assigned from three leading continents. The members scored >3500 published articles. Five meetings were held to complete the process. The guidelines were developed according to the AGREE Instrument II (*Appraisal of Guidelines for Research and Evaluation*) (18). It included the presented 132 statements and 87 recommendations in 31 chapters. Recommendations reflected not only the evidence in literature but also the view of the complete committee as expert opinion.

The macrostructures of five guidelines on groin hernias are given in Table 1.

COMMENTS

There are >40 upgraded recommendations in the new guidelines. The only downgraded recommendation is about the lower postoperative pain and reduction in chronic pain incidences after laparo-endoscopic repair of primary unilateral hernias in male patients. The evidence is considered as weak for recommendation.

Although the guidelines recommended mesh-based repairs for all inguinal hernias, Shouldice repair was also named as the choice of non-mesh repair. The true recurrence and postoperative chronic pain rates of Shouldice repair are required to be determined outside the Shouldice Hospital. Among mesh repairs, the Lichtenstein technique with a standard flat mesh still seems to be the best choice. On the other hand, laparo-endoscopic repair is recommended for the repair of primary bilateral hernias. Transabdominal preperitoneal (TAPP) and totally extraperitoneal (TEP) have similar efficiencies. More importantly, the concept of tailored surgery was emphasized in the guidelines. Type of hernia, surgeon's expertise and skill, resources of the institution, and preferences of the patients are

the factors influencing the selection of the best technique for each case (16).

There seems to be a consensus regarding groin hernias in women and femoral hernias in both genders. Laparo-endoscopic mesh repair is the best option for these conditions (18). Waiting is not recommended, and timely repair should be performed. On the other hand, day surgery is recommended for most groin hernia cases. It is best accomplished using local anesthesia. Figure 1 is produced to outline the algorithm for groin hernia in women and men according to the guidelines for groin hernia managements.

Guidelines are not legal documents or regulations, they are just recommendations. Strict adherence to guidelines is not always the case. Early studies on the effectiveness of guidelines concluded that guidelines might be unlikely to affect a rapid change in daily medical practice (19). Nevertheless, Grimshaw and Russell reviewed 59 articles published till 1990 and found that all but only four of the articles reported significant improvements after the introduction of guidelines (20).

Physicians and surgeons need to reach published guidelines to read and evaluate them before using their principles and recommendations in daily practice. Therefore, this kind of publication should be free for readers. The full text of *International Guidelines for Groin Hernia Managements* was available for download at www.herniasurge.com for free of cost until April 2018. Similarly, some clinical guidelines can be freely collected from the website of the official journals (21). However, the spread of each guideline may not be at the same rate. For example, a guideline for a general clinical subject such as prevention of thromboembolism has a higher chance to be visible, whereas other guidelines for specific problems in a branch of medical practice may not be as widespread. Guidelines for groin hernia management can be a typical example of the latter. Specific hernia surgeons, the followers of the international hernia meetings, and the subscribers of the hernia-related journals can meet the hernia guidelines earlier. However, groin hernia treatment is a very common procedure for almost all general surgeons, and it may be a duty of hernia surgeons to inform their colleagues about hernia guidelines.

Different institutions may create separate guidelines on the same subjects. There may be some minor or even major differences among them about the management and treatment of specific conditions (22, 23). Naturally, surgeons or physicians, personally or institutionally, prefer one of the recommendations in different sources. This does not seem to be the case for groin hernia guidelines. In fact, some members of the societies or associations who participated in the preparation of the newest guidelines are common. The *International Guidelines for Groin Hernia Management* is like a jointly updated guide book in a comprehensive way. It is a great work that provides surgeons solid recommendations on improving the outcomes of this very common surgery, although there are still some shortcomings. For example, some issues such as management of sportsman hernia were not included. This particular subject could have been evaluated as a specific aspect. The diagnosis and treatment of sportsman hernia were presented in the IEHS guidelines published in 2011 and its update in 2015 (13, 15). Therefore, one can use these publications as a good source for this subject. In addition, returning to different sports activities was not discussed in the new guidelines. Information about returning to sports and post-surgical rehabilitation can also be found in the IEHS guideline. However, discrimination among different branches of sports does not exist. Probably, the most frequently asked questions are about jogging, weightlifting, and swimming. Jogging and weightlifting are self-limited activities, and patients can drop the activity if they feel pain and discomfort, but swimming may be a safety issue regarding the risk of drowning. Therefore, surgeons and patients may need more detailed information about swimming. In fact, there is very limited published evidence about these specific subjects; therefore, it was not possible to make solid recommendations. Nonetheless an expert committee opinion would have been useful for the readers.

One of the main expectations of the surgeons from the guidelines is to find satisfying answers for the frequent questions from their patients. For example, driving after groin hernia repairs is a very common issue between surgeons and patients (24). Although the guidelines state that physical activity restriction is not necessary after uneventful repairs and that the patients can resume work and leisure activities within 3–5 days, with no increased risk of recurrence and complications, no specific recommendations are specified. In practice, advice on when to drive after groin hernia surgery may widely differ among surgeons. Ismail et al. (25) reported that recommended convalescence, by British surgeons, before patients resume driving reflected a wide spectrum from "same day as operation" to 6–8 weeks. Some verbal definitions were also used such as "as soon as you feel comfortable" or "as soon as you can do an emergency stop." A more recent survey from England also revealed that the time advised to return to driving ranged from 24 h to 6 w (26). A definition of "after being able to perform an emergency stop" was also mentioned in this publication. This parameter has been studied for spine and hip operations and some qualitative measurements about braking performance (27, 28). Indeed, emergency stop is a safety issue, and it may be useful to advice patients about testing themselves on applying the brake sharply without starting the engine. On the other hand, automatic transmission may be advantageous and provide an early return to driving for patients undergoing a unilateral left inguinal hernia repair. It was also reported in an observational study that laparoscopic repairs could have better outcome in terms of car driving over open surgery (29). Amid, from the Lichtenstein Hernia Institute, reported that the main concern about this issue was that the inertial force of an impact or sudden stop while driving could cause recurrence because a 6- to 8-week period was needed for healing of hernia defect (30). However, as he mentioned, this is not the case in the era of tension-free open and laparo-endoscopic repairs, and patients can return to normal daily activities, including driving. Amid also agreed with Ismail et al. (25) about developing national guidelines on this issue (30).

Today, chronic pain following inguinal hernia repairs is as important an issue as recurrence. The International Guidelines evaluated this problem in detail. For the first time, a guideline addressed the genetic disposition with typing; DQB1*03:02 HLA haplotype is mentioned in a table on risk factors for chronic post-herniorrhaphy inguinal pain. Nevertheless, this information did not exist in the text, and the working party

did not cite the related reference in the list. In fact, the evidence is obtained from the genetic typing study conducted by Dominguez et al. (31), which was published in 2013, and it was revealed that the DQB1 *03:02 HLA haplotype is associated with increased risk of chronic pain following inguinal hernia surgery.

Cancer development and carcinogenic materials are one of the main concerns of patients (32, 33). It is not unusual for surgeons to hear a question about the potential carcinogenic effects of hernia meshes. Furthermore, surgeons have been concerned about this frightening possibility. Being "non-carcinogenic" was included among the properties of the ideal prosthetic material (34). As mentioned in the guidelines, polymeric implants prepared as thin smooth films were possibly defined as carcinogenic to humans by The International Agency for Research on Cancer in 2000 (35). Nevertheless, the Hernia Surge Group did not find any adequate evidence about the carcinogenic potential of hernia meshes. Very recently, after the Hernia Surge meetings, Chughtai et al. (36) reported that mesh-based hernia repair was not associated with an increased risk of subsequent cancer development in men. They followed 53.409 male patients with inguinal hernia and found similar cancer development rates in comparison with the control subjects who underwent cholecystectomy for cholecystitis or cholelithiasis and primary knee arthroplasty for osteoarthritis. This novel and promising study with relatively long follow-up seems to be a good instrument for addressing patients' concerns.

The *International Guidelines for Groin Hernia Management* scrutinized the comparison of open and laparo-endoscopic techniques and made many statements and recommendations. In fact, the evidence for laparo-endoscopic repairs has been accumulating well. These techniques are recommended for bilateral, sportsman, femoral, and groin hernias in women. However, the working party mentioned a need for designing large RCTs for better comparison in primary unilateral inguinal hernia repair in male patients by surgeons who are experts in both these techniques. It may really be required, despite two recent studies that provide more information for this comparison. In 2014, Dhankhar et al. (37) reported that Lichtenstein repair with local anesthesia is as good as TEP under general anesthesia for uncomplicated unilateral inguinal hernia. Lichtenstein repair had shorter operating time, smaller mesh size, and lower cost (37). On the other hand, a larger study by Westin et al. (38) revealed that patients operated with TEP experienced less long-term postoperative pain than those operated with the Lichtenstein technique under local anesthesia. A limitation of this study might be the randomization conducted on the day of surgery by the operating surgeon. The randomization time is relatively close to the operation hour, and it is not clear whether the patients were completely informed about the advantages of the picked technique, whereas the guidelines recommend informing the patients that "*There are many different repair techniques in routine use with varying advantages and disadvantages. Your surgeon will discuss these and other issues with you.*" (16). It does not mean having a small conversation just before the surgery. Patel et al. (39) reported a very interesting observation that the majority of patients reported a perception that a laparoscopic repair was safer and quicker than open repair; open repair had a higher complication rate than laparoscopic treatment; laparoscopic repair had a quicker return to work; and laparoscopic repair was the only method that could be performed as a day-case procedure. It may be a consequence of some post-modern factors. It seems appropriate to create two groups where each technique is performed by its expert surgeons in its own optimal conditions: Lichtenstein repair under local anesthesia and laparo-endoscopic repair under general anesthesia. Surgeons in each group explain to their patients the advantages of the operative technique in detail with adequate time and attention. An independent monitor is included in the study; he/she may be a surgeon or an anesthesiologist with a special interest in algology. The monitor should observe the patients blindly, with no information about the operative technique used (40).

A shortcoming of the new guidelines is lack of recommendations for technical details of laparo-endoscopic procedures, whereas International Hernia Society guidelines has provided statements and recommendations about technical details and pitfalls of TAPP and TEP such as "*Safest and most effective method of establishing*," "*Trocar choice, placement and positioning*," and "*How does port positioning contribute to the technique of TEP repair.*" (13). Surgeons and residents who need information about these specific subjects can use the IEHS guidelines as a good source.

When the first EHS guidelines were published, the authors stated that a large number of questions remained unanswered. They listed 14 questions in this subheading. Indeed, all but one question was partially or completely answered in the last guidelines. There is still one question since then that is still unanswered: "*Are there non-operative options for treating an inguinal hernia*?" This hope was based on the definition of hernia as a collagen disease (41, 42). The possible treatment modalities influencing collagen synthesis such as or other than growth factors have not been found to be promising yet. So, this is still a "question for future," possibly not for the near future.

Another "question for future" in the EHS guidelines in 2009 was about the specialization on hernia surgery and specific centers (12). Today, hernia treatment is somewhat driving through two targets: individualization of the treatment for each patient and specialization for the surgeons. The former has been defined in the guidelines as "tailored surgery," and the latter has been discussed in the new guidelines in Chapter 23: Specialized centers and hernia specialist. The working party defined a hernia specialist as "*surgeon with mastery/expert-level hernia surgery skills who actively trains, educates, and performs research.*" The Hernia Surge Group has stated that individual case volume of a surgeon is more important than a center's case volume. Surgeon's high case volume reduces recurrence rate. More importantly, in practice, the *International Guidelines for Groin Hernia Management* recommends an expert hernia surgeon for the treatment of recurrent inguinal hernias, particularly after failed anterior and posterior repairs.

Antibiotic prophylaxis has always been an issue for groin hernia repairs. Guidelines and reviews do not recommend prophylaxis in elective open repairs (12, 16, 43). However, a very recent survey from the United Kingdom stated that almost half of the surgeons used routine antibiotic prophylaxis

(MacCormick). Interestingly, 95% of the participants in this survey believed that a new set of specific guidelines was required for this subject (44). It is recommended that antibiotic prophylaxis may be of benefit in high-risk environments, with wound infection rates of >5% (18). Some studies from large-volume reference hospitals in Turkey reported quite high infection rates after elective inguinal hernia repairs. Yerdel et al. (45) stated that wound infection rate was 9% in patients with no prophylaxis, and this rate could be decreased to 1% with single-dose intravenous ampicillin and sulbactam. Ergul et al. (46) reported that infection rate was reduced to 5% from 7% with 1 g intravenous cefazolin, but the difference was not significant. They believed that antibiotic prophylaxis could not ameliorate the complex circumstances in a trauma center/general hospital (46). Institutional approaches to improve the outcomes are required to reduce infection rates in groin hernia surgery.

Lastly, it is worth mentioning that there is a striking change in Chapter 2: Risk factors for the development of inguinal hernias in adults. With low-level evidence, tobacco use is given a factor that is inversely correlated with inguinal hernia incidence. This is a contradiction to the statement in the EHS guidelines published in 2009 (12). It concluded that smokers had an increased risk of inguinal hernia. There was a recommendation for smoking cessation as the only sensible advice that could be given for preventing an inguinal hernia development. Interestingly, the cited reference for the inverse correlation of tobacco use in the International Guidelines just reported that tobacco use history increased the chance of a groin hernia diagnosis (47). This point probably needs a reasonable explanation.

CONCLUSIONS

The *International Guidelines for Groin Hernia Management* is the most voluminous work for treatment options for groin hernia in adults. It answers most of the questions in the surgeons' mind. There is no conflict with previous guidelines, but recent information is gathered, and recommendations are produced. In general, Lichtenstein repair maintains its importance, particularly for unilateral primary inguinal hernias in men. On the other hand, laparo-endoscopic repairs have gained more support in certain conditions such as hernias in women, femoral hernias, and bilateral inguinal hernias. Spreading the guidelines may provide the surgeons with an up-to-date knowledge and may also be useful for better outcomes in groin hernia surgery.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 89-93
DOI: 10.5152/turkjsurg.2018.3596

Original Article

Surgical approaches for papillary microcarcinomas: Turkey's perspective

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ABSTRACT

Objectives: The incidence of papillary microcarcinomas, which are defined as thyroid cancers of <10mm in size, has been increasing in the last decade. Herein, we present internet-based questionnaire results performed by the Turkish Association of Endocrine Surgery with the aim to evaluate the perspective of the management of papillary microcarcinomas in Turkey.

Material and Methods: The user-friendly questionnaire consisted of 13 questions in total. These questions mainly addressed the surgical management of nodules and cancer of <1 cm in size. Patient management before, during, and after surgical intervention was also included; additionally, the "active surveillance approach" was questioned.

Results: There were 420 responders in total who were of multidisciplinary origin (endocrinologists, surgeons, nuclear medicine specialists, pathologists, and oncologists). Total thyroidectomy was the predominant treatment approach (65%) for the classical type of microcarcinoma limited in one lobe, whereas in cases of microcarcinomas incidentally diagnosed during hemithyroidectomy, complementary surgery approach was advised by 40% of the responders. The responders found capsule invasion (86%) and patient based management (94%) of high importance. The percentage of the responders who recommended radioactive iodine ablation in incidental cancers having no aggressive criteria was 51%. The survey participants that were against routine central dissection in these cases accounted for 73% of the responders. The recommendation of active surveillance (follow-up without any interventional therapy) was limited with 9% responders.

Conclusion: The results of the questionnaire demonstrated that there have been various choices in Turkey for the surgical treatment of the papillary microcarcinomas.

Keywords: Papillary microcarcinoma, Turkey, thyroidectomy

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Cite this paper as:
Makay Ö, Özdemir M, Giles Şenyürek Y, Tunca F, Düren M, Uludağ M, et al. Surgical approaches for papillary microcarcinomas: Turkey's perspective. Turk J Surg 2018; 34: 89-93.

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Received 28.08.2016; accepted 02.10.2016.

This study was presented at the "7th National Endocrine Surgery Congress", 2015, Antalya, Turkey.

INTRODUCTION

The incidence of 'papillary microcarcinoma' (PTMC), which is defined as papillary thyroid cancer with the diameter smaller than 10 mm, has gradually increased in the last 20 years (1). One of the most important causes of this increase is the detection of nodules in the thyroid gland during ultrasonography, computed tomography, magnetic resonance imaging, or positron emission tomography that are performed for extrathyroidal reasons (2). There are many controversial issues about the clinical importance of papillary microcarcinomas, which are generally found incidentally. The acceptance of PTMC as a subclinical disease, its not displaying progression, and not affecting survival constitute the main cause of these discussions (3). In this study, it was aimed to evaluate the approach to PTMC in our country.

MATERIAL AND METHODS

A questionnaire study was arranged by the Turkish Society of Endocrine Surgery through their website between August 2014 and October 2014. The announcement of the survey with a brief introduction writing was conveyed to all enrolled members by the means of the website of the Turkish Society of Endocrine Surgery. One month after the first electronic announcement, the members were sent a second electronic mail for reminding. The online survey, which would be applied with a computer-assisted questionnaire technique (SurveyMonkey®; Palo Alto, CA, USA), was reached to the members via electronic link address. In this way, the questionnaires were completed electronically and recorded automatically. The questions were prepared by considering the controversial subjects about the approaches to papillary microcarcinomas in literature and scientific meetings. This questionnaire, which was easy-to-use, consisted of 13 questions on nodules with a diameter of <1cm and cancer management. In addition, the participants were asked about non-surgical monitoring approach in cases of papillary microcarcinoma. Preoperative, intraoperative and postoperative patient management was also included in the questions. The participants to the survey were divided according to their disciplines.

The data collection, protection, and access were provided by the same computer-assisted software (SurveyMonkey®). This study was performed in accordance with the Declaration of Helsinki.

RESULTS

The questionnaire forms were completed by a total of 420 participants from 5 different disciplines including endocrinology, general surgery, nuclear medicine, pathology, and medical oncology. Of the participants, 57% were surgeons, 23% were nuclear medicine specialists, 18% were endocrinologists, 1% were pathologists, and 1% were medical oncologists.

The role of fine needle aspiration biopsy and primary treatment planning in detected cancer

The response to the question 'Do you recommend fine needle biopsy for an ultrasonographically suspected nodule with a diameter of <1cm?' was 'yes' by 89% of the participants and 'no' by 11% of the participants. Considering the study fields of the participants, while all of endocrinologists and nuclear medicine specialists responded as 'yes', 15% of general surgeons responded as 'no'.

When the participants were asked about their treatment suggestions for classical papillary carcinoma that was restricted with a single lobe and detected by fine needle biopsy, and had a diameter of <1cm, the views of 65% were in favor of total thyroidectomy, 33% in favor of hemithyroidectomy, 0.5% in favor of follow-up, and 0.5% in favor of ablation treatment [laser, radiofrequency thermal ablation (RFA), high intensity focused ultrasonography (HI-FU)]. When considered from the view of occupational groups, 78% endocrinologists recommended total thyroidectomy and 22% recommended hemithyroidectomy. Of general surgeons, 58% recommended total thyroidectomy and 40% recommended hemithyroidectomy. 1% of the surgeons presented their views in favor of follow-up and other 1% stated their views as ablation treatment. Of the nuclear medicine specialists who responded the question, while 71% and 24% recommended total thyroidectomy and hemithyroidectomy, respectively, 5% recommended follow-up (Figure1).

Completion surgery

To the question 'for a patient with a <1cm diameter papillary cancer incidentally detected after hemithyroidectomy, do you recommend completion surgery if residual lobe is ultrasonographically normal?', while 41% of the participants answered as 'yes', 59% answered as 'no'. While 11% of endocrinologists recommended completion surgery, 34% of general surgeons and 48% of nuclear medicine specialists recommended this surgery for a patient having these features.

For the question asking whether they recommended completion surgery even if residual tissues did not include nodule and pathological lymph nodule in patients undergoing subtotal thyroidectomy, while 34% of the participants replied in favor of completion surgery, 66% stated that they did not recommend. 11% of the endocrinologists, 30% of general surgeons, and 50% of nuclear medicine specialists recommended completion surgery (Figure 2).

Management according to the pathological features of specimen and patient

The question 'if you have recommended follow-up, does the presence of capsular invasion change your decision?' was answered as 'yes' by 86% of the participants and as 'no' by 14% of the participants. With regard to the occupational groups, 89% of the endocrinologists, 84% of the general surgeons, and 85% of the nuclear medicine specialists stated their views as 'I change my decision'.

For the question 'do you recommend radioactive iodine (RAI) ablation for a patient with classical papillary carcinoma including more than one foci smaller than 1 cm and without capsular invasion and lymph node metastasis?', 52% of the participants replied as 'yes, I recommend RAI ablation'. The answer was 'yes' by 32% of the endocrinologists, by 52% of the general surgeons, and by 58% of the nuclear medicine specialists.

While 94% of the participants answered as 'yes' for the question 'do you believe in patient-specific management (age, risk factors, pathology result, etc.)?', all of endocrinologists agreed on this view. On the other hand, 92% of the general surgeons and 90% of the nuclear medicine specialists specified that they believed in patient-specific management.

Molecular genetics

For the question 'does the occurrence of preoperative BRAF mutation (+) change your surgical treatment strategy?', the response of 67% was 'yes'. 74% of the endocrinologists, 66% of the general surgeons, and 61% of the nuclear medicine specialists answered as 'yes, I change my surgical strategy' (Figure 3).

Central dissection in papillary microcarcinoma

For the question 'should routine central lymph node dissection be performed intraoperatively in a patient with papillary microcarcinoma?', 27% of the participants said 'yes'. Of the endocrinologists, 78% defended that routine central dissection should be performed in patients with papillary microcarcinoma. However, 86% of general surgeons stated their views in favor of not performing routine central dissection in papillary microcarcinoma cases by answering as 'no'. Of the nuclear medicine specialists, while 50% replied as 'yes', other 50% answered as 'no' (Figure 4).

Active follow-up without treatment and ablation treatments in papillary microcarcinomas

For the question 'do you follow up papillary carcinomas with the diameter of <1cm without any treatment (by not applying surgery and/or RAI ablation)?', the response was 'no' by 91% of the participants and 'yes' by 9%. The response was in favor of follow-up without treatment by 11% of the endocrinologists, 8% of the general surgeons, and 18% of the nuclear medicine specialists.

For the question 'do you include ablation treatments (laser, RF, HI-FU) for microcarcinomas in your practice?', while 88% of the participants responded as 'no', 12% responded as 'yes'. While all of the endocrinologists stated that they did not include ablation treatments in their practices, 91% of general surgeons and 86% of nuclear medicine specialists agreed on the same answer.

Replacement treatment in the cases of papillary microcarcino*mas*

For the question 'after surgery, should <3 mm papillary cancer with a single focus be followed up or be given only replacement treatment by accepting it as an incidental cancer? ', while 66% of the participants replied as 'routine follow-up', 34% re-

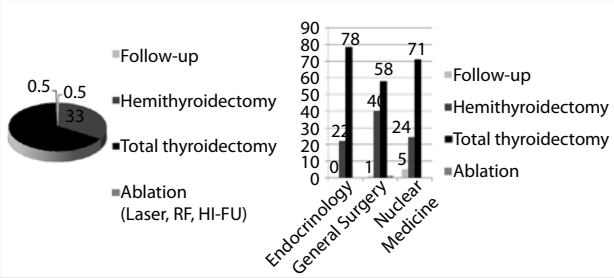

Figure 1. First treatment approach

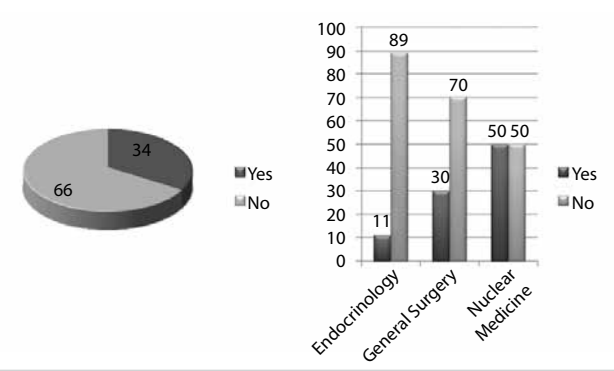

Figure 2. Completion surgery

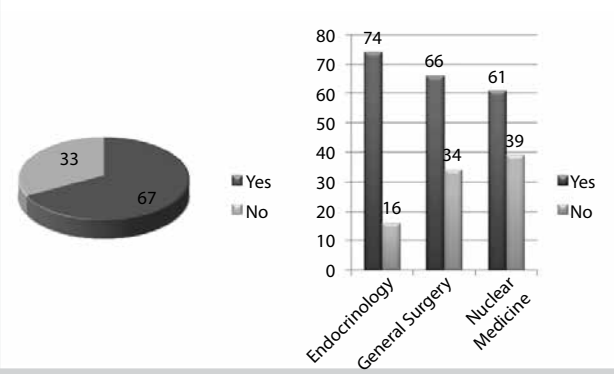

Figure 3. BRAF mutation (+), surgical treatment strategy

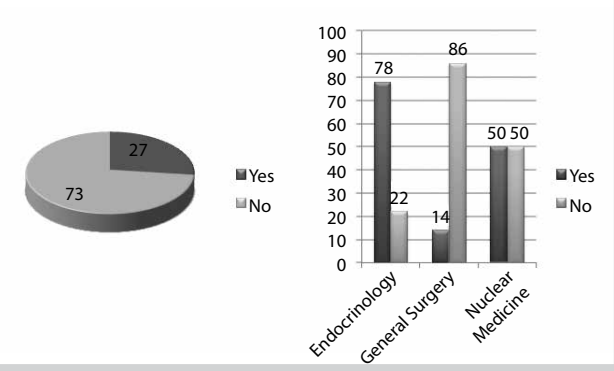

Figure 4. Routine central dissection in papillary microcarcinoma

plied as 'replacement treatment'. Considering their occupational groups, 89% of the endocrinologists, 69% of the general surgeons, and 67% of the nuclear medicine specialists stated their opinions in favor of performing routine follow-up.

DISCUSSION

The American Thyroid Association (ATA) guidelines, which were published in 2015, make sorting in terms of evidence value and give some recommendations. One of these recommendations is related to the management of nodules with the diameter of <1 cm. Here, because they only have higher malignancy potential, only nodules having a diameter over 1 cm should be evaluated and they should be performed fine needle aspiration biopsy according to their sonographic features (4). Besides that, the guidelines state that patients having suspected ultrasonographic findings, coexisting lymphadenopathy, history of radiotherapy to the head and neck, and a familial history of thyroid cancer in one of more first-degree relatives should be evaluated if their nodules are smaller than 1 cm. Of the specialists participating in this study, 89% stated that fine needle aspiration biopsy should be applied to ultrasonographically suspected nodules smaller than 1 cm.

Considering treatment suggestions for classical papillary cancer detected through fine needle biopsy and and restricted in a single lobe, there is no controversy on that the approach to patients with malignant result of cytology should be surgical. Then, which surgical procedure should be applied? If thyroid cancer is smaller than 1 cm and it does not have extrathyroidal spread, clinically metastatic lymph node, and a clear indication for the removal of the contralateral thyroid lobe, hemithyroidectomy would be sufficient. Hemithyroidectomy is reported to be an adequate treatment for small, unifocal, intrathyroidal carcinomas in patients without a history of radiation therapy on the head and neck, familial thyroid carcinoma, and clinically detected lymph node metastasis (4). While the ATA guideline published in 2015 recommends hemithyroidectomy for these patients, it also emphasizes that there are views defending that these patients can be followed up without any surgery as well as views defending the application of total thyroidectomy. In the hands of experienced surgeons, the rates of complications associated with total thyroidectomy are the same with those associated with hemithyroidectomy (5). In a study conducted by Hay et al. (6), PTMC patients performed hemithyroidectomy and total thyroidectomy were compared. In this study, for total thyroidectomy and hemithyroidectomy, local recurrence rates were reported to be 14% and 19% and lymph node metastasis rates to be 2% and 6%, respectively (6).

There are studies that recommend follow-up without any surgery to a patient group with clinically low risk. Particularly two prospective studies with Japanese origin are highly remarkable. In the study conducted by Ito et al. (7) from Kuma Hospital, 1235 patients with PTMC, the presence of which was proven by FNAB, were followed up without surgical treatment. 191 (15%) patients followed for 60 months on average were operated due to tumor growth or newly developed lymph node metastasis and no change was reported during their follow-ups (7). In the other study, Sugitani et al. (8) followed up 230 PTMC patients diagnosed with FNAB for about 5 years and they reported that surgery was required during follow-up only in 7% of these patients. Although the results are striking, further studies on larger series and with high evidence level are needed for the choice of follow-up to come into prominence.

If residual lobe is ultrasonographically normal in a patient with <1cm papillary cancer detected incidentally after hemithyroidectomy, should completion surgery be recommended? The conducted studies have shown that the rate of complica-

tions of completion surgery after hemithyroidectomy is the same with the rates in total or near-total thyroidectomy (9). Besides that, what is recommended for completion surgery in the guidelines is that: completion surgery is needed for cases whose first indication for surgery requires bilateral surgery (4). These cases are those having one of features including extrathyroidal invasion, multifocality, clinically positive central lymph node, history of radiation therapy to the head and neck region, and familial history of thyroid cancer.

In patients with clinically metastatic lymph node, the role of therapeutic lymph node dissection in the treatment of thyroid cancer is apparent. However, the value of routine prophylactic central lymph node dissection is controversial in patients without clinically proven metastasis in the lymph nodes (4). In the hands of experienced endocrine surgeons, central lymph node dissection has a course with low morbidity (10). Despite the applicability of prophylactic central dissection in T3 and T4 tumors, prophylactic central lymph node dissection is not recommended for T1 and T2 tumors by the updated ATA guideline (4).

An increase in the rates of extrathyroidal invasion, multi-centrality, and nodal metastasis is known to occur in the presence of BRAF mutation (11). Although BRAF mutation is encountered at the rates between 30% and 67% in PTMCs, its effect on recurrence is low as 1-6% (12). While there are views suggesting that surgical choice in the presence of BRAF mutation should be total thyroidectomy, some researchers defend that it should not be a single criterion for the decision of surgery (4, 13).

For multifocal or unifocal PTMCs, postoperative RAI treatment is not routinely recommended. In a multicenter study including 1298 patients with low-risk differentiated thyroid cancer, 911 patients undergoing RAI ablation treatment and 387 patients not undergoing RAI ablation treatment were followed up for about 10 years and it was demonstrated that RAI ablation treatment had no effect on disease-free survival (14). Moreover, in another study including 704 patients diagnosed with low and moderate-risk PTMC, 578 patients receiving RAI ablation therapy and 126 patients not receiving RAI ablation treatment were followed up for 64 months on average and it was found that RAI ablation treatment did not affect recurrence (15). Postoperative follow-up varies depending on the surgical procedures. Patients who have been treated with only lobectomy or total thyroidectomy without receiving radioactive ablation treatment should be followed with annual neck examination, ultrasonography, and serum thyroglobuline analysis. Similar method is used for patients undergoing total thyroidectomy and RAI ablation treatment. However, the sensitivity of serum thyroglobuline measurements becomes higher in such cases (16).

CONCLUSION

In this questionnaire study, it was aimed to evaluate the approaches of our colleagues to papillary microcarcinomas, the rate of which has increased with the development and more usage of diagnostic methods. In conclusion, it was observed that there were various views about the surgical management of papillary microcarcinomas and postoperative treatment in our country, as across the World. We suggest that more clear approaches to the treatment of this cancer will appear with further qualified studies on papillary microcarcinomas, as well as increasing number of patients and prolonged follow-ups.

Ethics Committee Approval: Not required in this study.

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.M., Y.G.Ş., M.U.; Design - F.T., M.D., M.U.; Supervision - M.H., G.İ., A.İ., S.Ö., Z.Ö., S.T.; Resource - G.İ., A.İ., S.Ö.; Materials - Ö.M., M.Ö.; Data Collection and/or Processing - Ö.M., M.Ö.; Analysis and/or Interpretation - A.İ., S.Ö., Z.Ö., S.T.; Literature Search - Ö.M., M.Ö., M.H.; Writing Manuscript - Ö.M., M.Ö.; Critical Reviews - Ö.M., Y.G.Ş., M.U., F.T., M.D.

Conflict of Interest: The authors has no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 94-96
DOI: 10.5152/turkjsurg.2018.3781

Original Article

Effects of body mass index on cecal intubation time in women

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ABSTRACT

Objective: During colonoscopy, cecal intubation time is prolonged with increase in difficulty of the procedure. Cecal intubation time may be affected by age, gender, and body structure. We investigated the relationship between body mass index and cecal intubation time in women.

Material and Methods: This prospective study included 61 women who underwent colonoscopy in the endoscopy unit of the General Surgery Clinic in Trabzon Kanuni Training and Research Hospital between January 2016 and September 2016. The colonoscopies were performed by a single surgeon. The height and weight of all the participants were measured, and their body mass index values were calculated before the procedure. The timer was activated as soon as entry was made from the anal region with colonoscope and stopped when the cecum was reached. The cecal intubation time was recorded for each subject. The results were evaluated statistically, and $p<0.05$ was considered to be significant.

Results: The mean body mass index was 29.6±6.8 kg/m^2. The median cecal intubation time was 4 min. (minimum 2 min; maximum 8 min). A significantly strong positive correlation was found between body mass index and cecal intubation time (r:-0.891, $p<0.001$).

Conclusion: Cecal intubation time was found to be shorter in women whose body mass index values were high. This outcome may help to eliminate the "the colonoscopy will be difficult" preconception, which is common among endoscopists with regard to the colonoscopies for obese female patients.

Keywords: Body mass index, cecum, colonoscopy, time

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Cite this paper as:
Karapolat B, Küçüktülü Ü. Effects of body mass index on cecal intubation time in women. Turk J Surg 2018; 34: 94-96.

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Received: 01.12.2016
Accepted: 03.03.2017

INTRODUCTION

Colonoscopy is widely used in the diagnosis of colorectal diseases and in the follow-up of their treatments of (1, 2). It is a safe procedure that is usually well tolerated with sedoanalgesia. Colonoscopy is used as a treatment modality in some colon diseases such as colon mucosal bleedings, polyps and luminal stenosis (3). Cecal intubation, an important factor in the evaluation of colonoscopy performance, is necessary to ensure that the colon examination is whole and complete (2). Cecal intubation time (CIT) describes the length of time in which colonoscopy reaches from the anal region to the caecum, and is a determining factor for difficult colonoscopies (4). It is reported in the literature that CIT is affected by advanced age, female gender, abdominal surgical history, diverticulosis, poor intestinal cleansing and by the colonoscopy experience of endoscopist (3, 4).

There is a significant relationship between the body structures of the patients and CIT (5). An ideal colonoscopy application and duration can be achieved in cases with optimal body mass index (BMI). Often, low circumference of the waist and little visceral fat tissue cause prolongations in the duration of colonoscopy. However, obese cases that are frequently encountered in everyday practice may pose a problem during colonoscopies for the endoscopists due to inadequate intestinal cleansing as well as phenotypic characteristics. It is also more difficult to perform maneuvers such as the application of abdominal pressure and new positioning during colonoscopy in obese patients, and this situation can lead to prolongation of colonoscopy (5).

The aim of this study is to identify the relationship between BMI and CIT in colonoscopy cases without different variables such as endoscopist's experience, adequacy of bowel cleansing and intraabdominal adhesions.

MATERIAL AND METHODS

Cases and study protocol

This study includes 61 female patients in whom colonoscopy was performed in the endoscopy department of General Surgery Clinic in Trabzon Kanuni Training and Research Hospital between January 2016 and September 2016. All of the cases were 18 years of age, and none of them had a history of abdominal

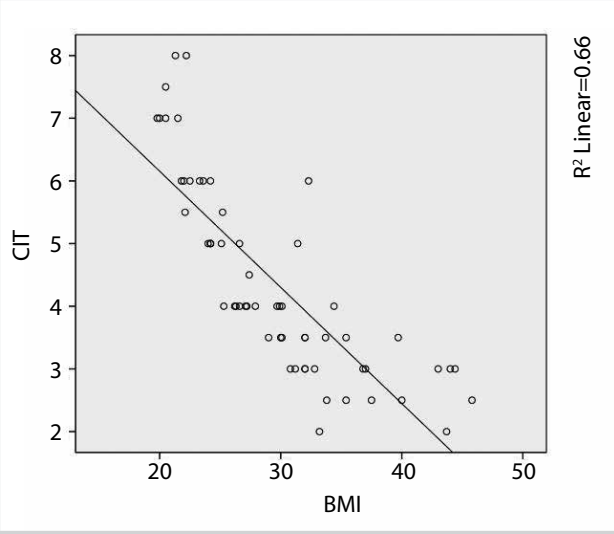

Figure 1. A strong positive correlation was found between BMI and CIT at a statistically significant level

operation. The most common indications for colonoscopy include constipation, anemia, intermittent inactive rectal bleeding, occult blood positivity in the stool, and polypectomy that was previously performed. Here, the cases who will undergo colonoscopy for therapeutic purposes, the cases with colostomy, the cases who had abdominal operation, the cases who had inadequate intestinal cleansing during the procedure, and the cases who rejected the administration of sedoanalgesia during colonoscopy were excluded from the study. Colonoscopy was performed by a single surgeon. It was suggested that the patients consume liquid food products and water 2 days before the procedure, and the intestinal cleaning was performed by using Sennozid a+b calcium (X-M solution Yenişehir Laboratory Ind. Trade. Co. Ltd., Ankara, Turkey) and BT enema (BT enema, Yenişehir Laboratory Ind. Trade. Co. Ltd., Ankara, Turkey). The patients were told not to eat and drink anything after midnight before the procedure, and they were enabled to come to the clinic hungry in the morning. Weights and heights of all the cases were measured by standard methods before the procedure, and their BMIs were calculated. This study protocol was approved by the local ethics committee and all cases were given sufficient verbal information, and they read and signed the written informed consent forms before the procedure. The work was carried out in accordance with the Helsinki Declaration principles, which were revised in 2000.

Colonoscopy procedure

Colonoscopy procedures were performed between 9.00 and 11.00 in the morning. Prior to colonoscopy, a vascular access was opened with a thick calibrated branule in the antecubital vein, and monitorization was performed for the pulse, blood pressure, arterial and blood oxygen saturations. Two liters/minute of nasal oxygen was given to all patients during the procedure and all medications were administered intravenously. Initially, midazolam (Dormicum ampoules, Roche, Istanbul, Turkey) was given at a dose of 0.05 mg/kg and meperidine (Aldol bulbs, Liba, Istanbul, Turkey) was given at a dose of 0.3 mg/kg. When necessary, additional doses were administered by the anesthesiologist according to the follow-up criteria of the case in the treatment process (maximum doses: 0.1 mg/kg for midazolam and 1.5 mg/kg for meperidine). All colonoscopy procedures were performed by a single surgeon with 10 years of colonoscopy experience after the cases received adequate sedation. When the anal region was entered with colonoscopy, the time was started and it was terminated when the caecum was reached. These CITs obtained are recorded for each case.

Statistical Analysis

All statistical data analyses were made using the SPSS 15.0 version package program for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics and Spearman correlation analysis were used here. The statistical significance level was accepted as $p<0.05$. The Spearman correlation analysis was performed to assess the relationship between BMI and CIT.

RESULTS

All the cases in this study were female. In the investigation of etiology; constipation and rectal bleeding, which are the indications of colonoscopy, were found to be in the first place with the rates of 29% and 22%, respectively. The youngest patient was 18 years old and the oldest was 81 years old; the mean age was found as 47.7±14.6 years. The lowest BMI was 19.8 kg/m^2 and the highest BMI was 45.8 kg/m^2. The mean BMI was 29.6±6.8 kg/m^2. Colonoscopy was performed successfully in all cases and no complication occurred. The median CIT was 4 min. (minimum 2 min - maximum 8 min). There was a strong positive correlation between BMI and CIT at a statistically significant level (r: -0.891, $p<0.001$) (Figure 1).

DISCUSSION

Over the years, the relationship between the body weight and the technical difficulties encountered during colonoscopy has been a matter of serious debate, especially in the stage of reaching the caecum. There are different data in the literature indicating that weak or obese patients cause difficulty for the endoscopist during colonoscopy (3, 4). In fact, obesity is considered to be an independent factor that causes difficult and long colonoscopy and is associated with poor intestinal cleansing (5). If CIT is prolonged during the colonoscopy; discomfort, respiratory depression, low oxygen saturation, hypotension, cardiac arrhythmia, aspiration, malignant hyperthermia and allergic reactions may occur. It should be kept in mind that these undesired conditions may depend on the medicines and/or materials used. In addition, rare serious complications related to barotrauma, such as mucosal tears, intestinal perforation and air embolism, may also be seen (6). Therefore, the total length of colonoscopy and the importance of CIT have increased even more in obese cases, potentially bearing the risk of complications.

In this study, a number of limiting variables have been eliminated to evaluate the relationship between the duration of colonoscopy and body weight. For this purpose; the patients in whom colonoscopy would be performed for treatment, the patients with colostomy, the patients who underwent abdominal or pelvic surgery, the patients with inadequate bowel cleansing during the procedure, the patients who rejected sedoanalgesia during colonoscopy, and the patients in whom colonoscopy was performed by the other endoscopists in our clinic were not included in our study. Thus, a homogeneous

patient group which completely consisted of female patients and operated by a single endoscopist was used and the external effects were tried to be minimized.

The BMI is a commonly used parameter for defining the body weight. However, BMI does not give a definitive information about the accumulation of fat in the retroperitoneal area and in the abdomen. In fact, these regions with fat accumulation are best displayed with abdominal computed tomography (7). However, it does not seem to be possible to take tomography in all cases in practice, considering both unnecessary radiation exposure and cost (5). For this reason, we preferred to use BMI, which is the most harmless and easiest way to define the body weights of colonoscopy cases included in this study. In the result of our study, a strong positive correlation at a statistically significant level was found between BMI and CIT in women. It was revealed that CIT was shorter in cases with higher BMI. The results obtained are consistent with the literature (4, 8-10). It is known that there is somewhat more fat accumulation in the retroperitoneal area of the women with higher BMI than those with normal BMI. We believe that stored fat pads in this area may cause the colonoscope to move smoothly at sharp curves during the colonoscopy procedure and shorten CIT. At the same time, the fact that overweight patients have relatively shorter colon than the normal population can also provide an additional contribution to the shortening of CIT (4, 11).

As a general opinion, endoscopists believe that they may encounter difficulties in the procedures in obese patients and that the duration of endoscopy may be longer than it should be (5). However, in this study, we have obtained data showing that the duration of endoscopy is shorter in obese women than in other cases. In terms of preventing the false beliefs and concerns mentioned above, we think that these results may be important for endoscopists interested in colonoscopy.

In a prospective study conducted by Bernstein et al, it has been reported that extended CITs occur due to the factors such as advanced age, female gender, low BMI, poor intestinal cleansing, and low number of annual cases of endoscopists (12). One of the important factors affecting CIT is the colonoscopy experience of endoscopists (2, 12, 13). As in many medical applications, endoscopists gain experience with the number of procedures they perform and the difficulties-complications they encounter during the procedure of colonoscopy and with successful control and management of these difficulties. It is therefore evident that CIT averages achieved by an experienced endoscopist during colonoscopy will be much shorter. We think that the CIT of colonoscopies performed by different endoscopists will vary depending on the experience, and this situation can affect the homogeneity of the clinical trial. For this reason, colonoscopies were performed by a single endoscopist in our study and, the factor of endoscopist occurring due to the changing experiences and abilities was eliminated.

This study has a number of limitations such as the fact that it has been performed in one center, the number of cases is low and only female cases have been evaluated. We think that the results obtained here can gain more value in the future with multi-centered studies using larger populations.

CONCLUSION

Cecal intubation time was found to be shorter in women with higher BMI. This may help eliminate the prejudice of "colonoscopy will be difficult", which is a widespread opinion about colonoscopy in obese female patients.

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".

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.K.; Design - B.K., U.K.; Supervision - B.K., U.K.; Resource - B.K.; Materials - B.K., U.K.; Data Collection and/or Processing - B.K.; Analysis and/or Interpretation - B.K., U.K.; Literature Search - B.K.; Writing Manuscript - B.K.; Critical Reviews - B.K., U.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 97-100
DOI: 10.5152/turkjsurg.2018.3755

Original Article

Importance of informed consent defined by General Surgery Associations in Turkey

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ABSTRACT

Objective: Informed consent is a term based on the idea that every individual has the right to know every medical intervention that is going to be performed on their own body and to learn the issues that she/he may encounter in case of refusal of intervention, and it also defines the protection of personal rights under the guarantee of law.

Material and Methods: The website of Turkish Surgical Association and 25 different websites of surgical associations were evaluated according to general surgery association guide, which was published by the Turkish Surgical Association in 2011.

Results: Four websites of those surveyed include informed consent sections and these were evaluated. A total of 44 informed consent forms were included in this study. Of these, 29 were in Turk Colon and Rectum Surgery Association, 8 were in Turkish Surgery Association, 5 were in Turk Hepatopancreaticobilier Surgery Association, and 4 were in Endocrine Surgery Association. These informed consent forms were evaluated with regard to the aforementioned criteria. The results and also the distribution according to the associations were summarized. A common feature of the informed consent forms was that all of them included the risks of the intervention/operation and complications to be carried out. On the contrary, none of them included approximate time of surgery, information about surgeons, issues that patients should care about before surgery, the section that permits the use of data for scientific purpose, and the time of signing the informed consent form.

Conclusion: We believe that in this context the regulation of informed consent by sub-specialization associations under the flag of Turkish Surgical Association is a very important matter and will standardize informed consents; websites of the associations will be easier to access, and this will be as beneficial for physicians as the patients and also will protect the physicians in probable trials.

Keywords: Association, form, importance, informed consent, surgery

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Cite this paper as:
Kamer E, Tümer AR, Acar T, Uyar B, Ballı G, Cengiz F, et al. Importance of informed consent defined by General Surgery Associations in Turkey. Turk J Surg 2018; 34: 97-100.

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This study was presented at the "20. National Congress of Surgery", 13-17 April 2016, Antalya, Turkey.

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Received: 03.11.2016
Accepted: 20.03.2017

INTRODUCTION

Informed consent (IC) expresses the concept in which an individual understands all medical interventions to be performed in him/her based on his/her own free choice without any external coercion, and on learning the problems to be encountered if he/she does not accept these interventions, and it also expresses the concept in which personal rights are assured with the laws regulated on this issue (1).

In the informed consent form (ICF), it is necessary that the information should be explained clearly enough for the patient to be informed so that the patient can make a decision about himself/herself. In addition, the ICF should also give the patient information which includes the benefits and risks of the recommended treatment, the alternatives to the treatment if any, and the consequences in the case that he/she rejects the treatment. In order for the consent to be valid, it is necessary for the patient to be informed about the medical intervention to be applied by the physician who will perform the treatment and to understand the information given. Based on the Article No. 70 of the Law No. 1219, only one form, which is still in practice today, is not regarded as the patient's informed consent (2). The consents received without informing are legally invalid. There are different opinions between ethics experts and legal experts regarding the amount of information to be given to the patient. While ethics experts leave the amount of information to the doctors, legal experts recommend that this level be determined by law (3). The generally accepted recommendation is that the physician who will treat the patient enlightens the patient about the medical intervention to be performed, considering the patient's physical, sociocultural and personal beliefs and values (4). There are many studies conducted on informed consent in Turkey (1-6). However, we have not encountered a study that examines the websites of associations and investigates the suitability of ICFs on these websites.

We have planned to conduct a research on whether or not the information that is required to be found in ICFs in the light of the above information is included in the informed consents published on the websites of the general surgery associations, or on how much of it is included.

MATERIAL AND METHODS

According to the 2011 Guide of Turkish Surgical Association general surgical associations, there are a total of 26 general surgical associations, including Turkish Surgical Association in Turkey. Ethics committee approval was received for this study from the ethics committee of our hospital. One of the associations published in this guide was a federation which had 13 associations. According to this, a total of 38 internet pages have been examined. When the key words "consent" or "informed" were searched in the IC section or in the "search" button, such information could not be found in the websites of 34 (89.5%) associations. IC section was found and examined in four (9.1%) of the websites. These associations were Endocrine Surgical Association, Turkish Society of Colon and Rectal Surgery, Turkish Society of Hepato-pancreato-biliary Surgery and Turkish Surgical Association. The ICFs under the name of "general consent" that were not prepared specifically to the disease and the ICFs for colonoscopy were not included in the study. According to this, six ICFs from the Turkish Society of Colon and Rectal Surgery and one ICF from the Turkish Surgical Association were not included in the study. The criteria to be found in the informed consents were edited based on the data in the "Guide of regulations and informed consents for Physicians and Medical Chamber Executives" by a forensic medicine academician (Tümer A.R.) (7, 8). Number and percentage were used for the descriptive statistics.

RESULTS

IC section was found in four (9.1%) of the websites. A total of 44 ICFs, four of which were from the website of Endocrine Surgical Association, 27 from the website of the Turkish Society of Colon and Rectal Surgery, five from the Turkish Hepato-pancreato-biliary Society and eight from the website of the Surgical Society, were included in the study. There was no part for the personal identifying information of the patients in eight (18.2%) ICFs. In 36 of the ICFs (81.8%), a special part was found, usually located near or below the head of the form, where the personal identifying information of the patient would be written. A box where the patient's name, surname, date of birth, gender, protocol number, scheduled surgery and the diagnoses would be written was found in four ICFs; a box where the patient's name, surname, date of birth, protocol number, the date of hospitalization, and the diagnosis would be written was found in 27 ICFs, and a box where the patient's name, surname and protocol number would be written was found just under the heading in 5 ICFs. Only six (13.6%) of the ICFs had the information about the patient's disease, and nine (20.5%) had the information about the surgery/intervention to be applied and a statement explaining its purpose. In all of the ICFs (100%), there was somewhat information about the risks of the operation, and the complications-undesirable negative results. None of the ICFs had an explanation about the duration of the operation, about the doctor who would perform the surgery, about the things that the patient should be careful about before the operation, and about the permission for the data to be used in scientific studies. Five (15.9%) of the ICFs had the points that the patients should take into consideration after the operation; five (11.4%) of them had the information about the alternatives of the recommended treatment, if any; one of them had the information about the potential results of the recommended treatment; five (11.4%) of them had the information about the risks that could occur if the treatment is rejected. Twenty-four (54.5%) of the ICFs had the information about the anesthesia method to be applied in the patient (only the name is mentioned in 19 of them: such as "general anesthesia" or "local anesthesia") and the risks associated with this anesthetic method were indicated in 36 (81.8%) of them. Only eight (18.2%) of the ICFs had a section in which

Table 1. Distribution of ICFs of the associations according to the criteria

	A (n=4)	B (n=8)	C (n=5)	D (n=27)	Total (n=44)
A- Personal identifying information of the patient	4	0	5	27	36 (81.8%)
B-Information about the patient's disease	4	0	2	0	6 (13.6%)
C- Information about the surgery/intervention to be performed and its purpose	4	0	3	2	9 (20.5%)
D- The risks of surgery and undesired consequences/complications	4	8	5	27	44 (100%)
E- Duration of operation	0	0	0	0	0
F-Information about the doctor who will perform the operation	0	0	0	0	0
G-Things the patient should pay attention to before the operation	0	0	0	0	0
H-Things the patient should pay attention to after the operation	4	0	0	3	7 (17.9%)
I-Alternatives of the recommended treatment, if any	0	1	4	0	5 (11.4%)
J-Potential consequences of the recommended treatment	0	1	0	0	1 (2.3%)
K-The risks that may arise if the treatment is rejected	2	0	3	0	5 (11.4%)
L-Information about the anesthesia method to be applied	4	3	0	17	24 (54.5%)
M-The risks of the anesthetic method to be applied	4	6	0	27	37 (84.1%)
N-Permission to use the data in scientific studies	0	0	0	0	0
O-The Part where the name of the patient-witness and doctor will be written	4	2	5	0	8 (18.2%)
P- Date when informed Consent is received	4	6	5	27	42 (100%)
Q- Time when informed Consent is received	0	0	0	0	0

A: Endocrine Surgical Association; B: Turkish Surgical Association; C: Turkish Society of Hepato-pancreato-biliary Surgery; D: Turkish Society of Colon and Rectal Surgery

the names of the patient-witness and the doctor were written. In this last part, the information of the date was indicated in 40 (% 90.9) ICFs and the information of the time was indicated in only three (% 6.8) of them (Table 1).

DISCUSSION

Today, the ethical and legal aspects of informed consent is still being discussed by various organizations. Especially the legal regulations on IC and the corresponding sanctions are given particular importance in this discussion (1, 2, 7). As these debates continue, there is still no consensus on the information that should be in an ICF. The Article 26 of the Ethical Rules of Medicine states that "by paying attention to the cultural, social and psychological condition of the patient, he/she should be informed about his/her health status, the diagnosis that is made, type of the recommended treatment, the success rate and duration of the treatment, the risks of the treatment for the patient's health, the use of medicines given and possible side effects, the consequences of the disease if the patient does not accept the recommended treatment, and the possible treatment options and their risks"(8). The Article 31 of the Regulations on Patient Rights, it is simply stated that "While receiving the consent, it is essential to inform the patient or his/her legal representative about the medical intervention and its outcomes" (9). As it can be seen, there is no standardization about the information that must be found in an ICF. It has been stated in the guide prepared by the American Medical Association that the prediagnosis or diagnosis of the patient, the purpose of the recommended treatment, the risks and benefits of the recommended treatment, the alternative treatment methods if any, the benefits of the alternative treatments and their risks if any, and the natural course and risks of the disease if the patient does not accept the treatment should be included in an ideal ICF (10). The issue of adapting foreign-based ICFs to our country is another issue that needs to be discussed. However, when we examine the study of Güzeldemir, we can see that the information that must be found in a standard ICF covers the information in the guide of the American Medical Association. In the study of Güzeldemir, it is stated that a standard "Informed Consent Form" should include the diagnosis, the causes of the disease, the course of the disease, the structure and purpose of the recommended treatment or application, the duration of the anticipated intervention, the risks, complications and outcomes of the recommended treatment or application, the alternative treatment options to the recommended treatment or application, the results that the disease may cause if the recommended treatment or application is rejected, the benefits and expected results of the treatment if the recommended treatment or application is accepted, the information about the person to perform the treatment or application, and the medical fee (3). Here, the most remarkable parts are "the duration of the anticipated intervention, the person to perform the application and the medical fee". According to the study of Tümer; the points that should be included in an ICF are the diagnosis of the disease, the content of the treatment recommended to the patient, the aim of treatment and the chance of success, the risks of the recommended treatment and alternatives if any, the potential outcomes of the treatment, problems that the patient may encounter if he/she does not accept the treatment, the time required for the patient to return to normal life, the features of the drugs that the patient will use (such as duration, usage, side effects, interactions with other drugs), what the patient should do at home after treatment, how he/she will access medical aid for the same cause, personal identifying information of the person who will carry out the treatment, and his/her experiences on this subject (11-13). As is seen, considering the points that should be included in an ICF, there are differences in four studies, one of which is foreign-based.

According to the "Guide of regulations and informed consents for Physicians and Medical Chamber Executives", the information given to the patient should include the patient's diagnosis, information about health status, the recommended treatment method, the success and possible risks of this treatment method, the use and possible side effects of the given drugs, problems that the patient may encounter if he/she does not accept the treatment, alternative treatment options and the risks of these options.

Nowadays; although the importance of IC for both patient and physician has increased in the light of this information, there is not a parallel increase in the importance given to this subject. When the point of view of the general surgery associations on the fact of IC, which has been known for about 17 years, was examined, it was seen that this matter should be emphasized once again (12).

We see that the Turkish Surgical Association is an association that connects a truly great community which consists of 38 associations. The websites of most of these associations are actively working. On this site, it is possible to reach a lot of information about the association, scientific activities of the association, courses, scholarships, and links to the journals which they are affiliated to. These sub-branch associations under the Turkish Surgical Association have an effective and active role in their own branches.

It was seen that only 9.1% of these associations prepared ICFs according to their sub-branches and put them in their internet sites. Considering the diseases covered by the General Surgery and their surgical treatment, this ratio is very low. Moreover, it was seen that the ICFs that were found did not have most of the required information. The common characteristics of ICFs were that although the risks associated with the intervention/operation to be performed and the undesired negative consequences-complications were written in all of them, the approximate duration of the operation, the information about the doctor who would perform the surgery, the things that the patient should pay attention to before the operation, and permission for the use of data in scientific studies were not included in any of them. It is remarkable that the associations show a considerable indifference and insensibility about the IC, which is a really important issue in legal and humanitarian terms.

When we write "informed consent for …… disease" in search engines independently of associations, we see dozens of different ICFs belonging to a disease. In other words, we see that individuals or organizations prepare disease-specific ICFs according to themselves. It is a matter of debate how protective the use of these non-standard or non-legal forms is against the law (13).

On the other hand, getting only one form signed, which is still being applied today, is not regarded as the patient's informed consent (1, 12). It is essential that the patient should be informed in order for the consent to be valid. Today, the Constitutional Court has considered that an operation performed without the written informed consent of a person as well as an insufficient information and even the inability to prove that the patient has been informed are a violation of right (Y13.HD 2008 / 10750th Decision) (14). The physician has the burden of proof with regards to the fact that the informing has been done. It is natural that the physician assumes the burden of proof because the physician should actually have related documents and carry out the enlightenment procedure. In Ersoy's study; while most surgeons stated that they enlightened their patients, the fact that most of the patients stated that no explanation was given to them and that most of the patients had no information about the medical intervention that would be applied to them indicated that the people who would apply the medical intervention were not successful in providing the necessary amount of information and understanding (4).

CONCLUSION

Briefly, "Informed consent" is the process in which the patient gives the authority to use the medical facilities to the physician who will apply the treatment as the case may be, as a result of the formation of a human relationship between the patient who will be treated and the health worker who will perform the treatment.

A standard ICF should certainly include the parts of patient's personal identifying information (name, surname, protocol number, phone number), the diagnosis of the disease, information about the disease, information about the surgery/intervention to be performed and its purpose, the risks of operation/intervention and undesired negative consequences-complications, approximate duration of the surgery, information about the doctor who will perform the surgery, the things that the patient should pay attention to before and after the operation, the risks that the patient may encounter if he/she does not accept the treatment, information about the anesthetic method to be applied, the risks of the anesthetic method to be applied, permission for the use of data in scientific studies. In the last part of the ICF, the name and surname of the patient, the name and surname of the witness and the name and surname of the doctor who gives the information, and the date and time when the information was given should certainly be included.

All information in the ICF should be explained in accordance with the sociocultural level of the patient.

In lawsuits commenced for compensation by the patient and/or relatives, the fact that the patient is not sufficiently informed, that an appropriate IC is not received or the lack of IC put the physician in a difficult position before the law. In this context, we believe that the proper arrangement and publication of ICFs by sub-branch associations under the roof of Turkish Surgical Association will provide sufficient information about the procedure to the patient, protect the physicians in possible lawsuits and bring a standardization to this issue.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İzmir Katip Çelebi University, Atatürk Training and Research Hospital.

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

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

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 101-105
DOI: 10.5152/turkjsurg.2017.3740

Self-expandable metallic stent application for the management of upper gastrointestinal tract disease

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ABSTRACT

Objective: The aim of the present study was to share our experiences of the use of self-expandable metallic stent for the upper gastrointestinal tract disease.

Material and Methods: We retrospectively reviewed the medical records of 18 patients who underwent self-expandable metallic stent implantation procedure for anastomosis stricture, anastomosis leak, or spontaneous fistula of the upper gastrointestinal tract at two different surgery clinics. Self-expandable metallic stent implantation procedures were performed while keeping the patient under sedation and the correct stent localization was verified using fluoroscopy. The stent localization and possible stent migration were checked using X-ray films taken a few days after the stenting procedure.

Results: Overall, 25 self-expandable metallic stents were implanted in 18 patients (malignant, 13; benign, 5) aged between 19 and 89 years. The indications for self-expandable metallic stent implantation were as follows: malignant gastric stricture (inoperable; n=6), malignant esophageal stricture (inoperable; n=4), staple line leak (laparoscopic sleeve gastrectomy; n=4), esophagojejunostomy anastomotic leak (total gastrectomy+Roux-en-Yesophagojejunostomy; n=2), and stricture (total gastrectomy+Roux-en-Yesophagojejunostomy; n=1), and esophagopleural fistula (pulmonary tuberculosis; n=1). A favorable outcome was achieved in a single session in 15 patients, whereas more than two sessions of stenting were necessary in the remaining three patients. Among the patients who underwent esophagojejunal anastomosis (n=3), self-expandable metallic stents were successfully deployed in a single session in two patients to relieve anastomosis leak (n=1) and anastomosis stricture (n=1); the remaining patients underwent four self-expandable metallic stent implantation procedures to relieve anastomosis leak and subsequent recurrent strictures. No complications developed during the stenting procedure. Three of the four patients who developed mortality had advanced stage esophageal cancer, whereas one patient had morbid obesity and developed staple line leakage.

Conclusion: Endoscopic self-expandable metallic stent implantation under fluoroscopic guidance is a low-morbidity and effective procedure for the management of advanced stage tumors of the gastrointestinal tract and the elimination of postoperative complications.

Keywords: Leakage, metallic stents, stenosis, upper gastrointestinal tract

Cite this paper as:
Emre A, Sertkaya M, Akbulut S, Erbil O, Yurttutan N, Kale İT, et al. Self-expandable metallic stents for upper gastrointestinal tract disease: Clinical experiences. Turk J Surg 2018; 34: 101-105.

This study was presented at the "33. National Gastroenterology Week, "22-27 November 2016", "Antalya, Turkey".

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Received: 19.10.2016
Accepted: 18.05.2017
Available Online Date: 30.04.2018

Available online at
www.turkjsurg.com

INTRODUCTION

Until the last quarter century, many treatment modalities, particularly the surgical ones (open/laparoscopic), have been used for the primary management of some benign and malignant conditions of the upper gastrointestinal tract and their complications (1-4). Owing to recent technological advances in endoscopic devices and the introduction of novel stent materials, the endoscopic approach has become the first option (1, 4-7). This approach has been widely used owing to its minimally invasive nature and feasibility under mild sedation (8-16). The aim of the present study was to share with the readers our experience of using self-expandable metallic stents (SEMSs) for the treatment of complications involving the upper gastrointestinal tract, such as fistula and stricture.

MATERIAL AND METHODS

We retrospectively reviewed the demographic, clinical, endoscopic, and radiological records of 18 consecutive patients who underwent SEMS implantation (Hanarostent, M.I. Tech Co. Ltd., Pyeongtaek, South Korea) for malignant disorders and benign complications (anastomosis stricture, anastomosis leak, and spontaneous fistula) affecting the upper gastrointestinal tract at the Department of Surgery, Sutcu Imam University Faculty of Medicine, Kahramanmaras and Department of Surgery, Gebze Fatih State Hospital, Izmit, Turkey. All SEMS implantation procedures were performed by two independent surgeons (AE and OE) experienced in endoscopy, fluoroscopy, and endoscopic stenting. Depending on the area and region of complication, stents with various characteristics were used. The technical characteristics of the stents used in this study are as follows: a 210-mm long Hanarostent® Esophagus Bariatric Surgery (ECBB-28-210-090) stent was used for 4 cases with leaks at stapler line after bariatric surgery. A 100-mm long Hanarostent® Esophagus Benign BS (CCC) (EBN22080-Z070) stent was used for complications with esophagojejunostomy anastomosis

Table 1. Demographic and clinical characteristics of 18 patients treated with self-expandable metallic stents

No.	Age	Gender	Underlying cause	Performed surgery	Stent indication
1	37	Male	Gastric cancer	Total Gastrectomy + Roux-en-Y Esophagojejunostomy	Esophagojejunostomy anastomotic leak
2	61	Male	Esophageal cancer (S:IV)	No	Malignant esophageal stricture
3	71	Male	Gastric cancer	Total Gastrectomy + Roux-en-Y Esophagojejunostomy	Esophagojejunostomy anastomotic leak
4	33	Female	Gastric cancer	Total Gastrectomy + Roux-en-Y Esophagojejunostomy	Esophagojejunostomy anastomotic stricture
5	36	Female	Pulmonary tuberculosis	No	Esophagopleural fistula
6	53	Male	Esophageal cancer (S:IV)	No	Malignant esophageal stricture
7	19	Female	Morbid obesity	Laparoscopic sleeve gastrectomy	Staple line leak
8	34	Female	Morbid obesity	Laparoscopic sleeve gastrectomy	Staple line leak
9	46	Male	Morbid obesity	Laparoscopic sleeve gastrectomy	Staple line leak
10	21	Male	Morbid obesity	Laparoscopic sleeve gastrectomy	Staple line leak
11	67	Male	Gastric Cancer (Antrum)	No	Malignant gastric stricture
12	80	Female	Gastric Cancer (Antrum) (S:IV)	No	Malignant gastric stricture
13	71	Female	Gastric Cancer (Antrum) (S:IV)	No	Malignant gastric stricture
14	62	Female	Gastric Cancer (Antrum) (S:IV)	No	Malignant gastric stricture
15	51	Male	Gastric Cancer (Antrum) (S:IV)	No	Malignant gastric stricture
16	74	Female	Esophageal cancer (S:IV)	No	Malignant esophageal stricture
17	89	Female	Esophageal cancer (S:IV)	No	Malignant esophageal stricture
18	59	Female	Gastric Cancer (Antrum)	No	Malignant gastric stricture

S: Stage

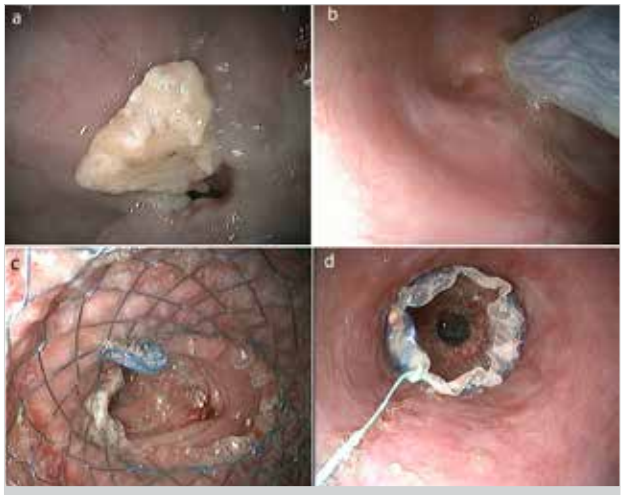

Figure 1. a-d. Some images of the stent implantation stage in patient with esophagial stricture secondary to cancer

after gastric cancer surgery. A 70-mm long and a 140-mm long Hanarostent® Esophagus Skid proof (ECD-20-180-070 and ECD-20-120-070) stents were used for 4 cases with malignant esophageal stricture. A 100-mm long Hanarostent® Esophagus Benign BS (CCC) (EBN22080-Z070) was implanted in a case with benign esophagopleural fistula. All patients who were scheduled for SEMS implantation procedures were fasted overnight before the procedure. Antibiotics were administered to all participants prior to the procedure. The stenting procedure was performed at the operating theater under sedation. Following the placement of a stent under endoscopic guidance, fluoroscopy was used to verify correct stent localization. Implantation of a stent to a correct position was defined as technical success. Complete elimination of the complication (stricture, fistula and leak) after stenting was defined as clinical success. Persistence of complications or death secondary to the persistence of complications despite stenting was defined as clinical failure.

X-ray imaging and endoscopy were performed one or a couple of days after the stenting procedure to check correct stent position and/or if migration occurred. Patients with appropriate stent localization were fed orally after 2–3 days of the procedure. In patients presenting with any gastrointestinal discomfort after discharge, one or a combination of examination findings, laboratory tests, radiological studies (plain radiographs and CT), and endoscopic examination were performed to check whether any stent-related complication developed. Eight out of 10 patients received temporary stents, whereas 2 received permanent stents. Time of stent removal was determined based on the time of elimination of complications and patient satisfaction. Quantitative variables were stated as mean±standard deviation and range (minimum–maximum), and qualitative variables were given as number with percent.

This study was conducted according to the Declaration of Helsinki and local approval was obtained from Kahramanmaraş Sütçü İmam School of Medicine Ethics Committee. Informed consent was obtained from all patients.

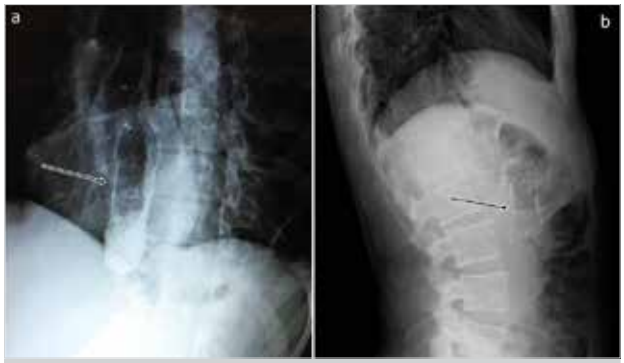

Figure 2. a, b. Radiologic appearance of stent migration to 3rd part of duodenum

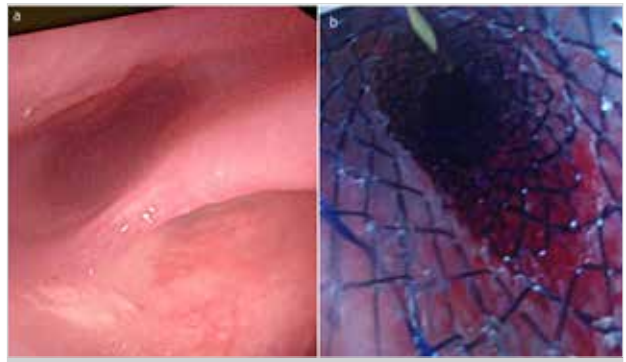

Figure 3. a, b. Management of patient with esophagopleural fistula

Table 2. Properties of the applied stents and outcomes of the 18 patients treated with self-expandable metallic stents

No	Type of stent	Length of Stent (mm)	Interval Between Stenting and Operat	Migration	Restenting	Additional Application	Outcome
1	Covered Metalic	100	3	Yes	Yes*	Dilatation + Submucosal steroid	Alive
2	Covered Metalic	140	No-operated	No	No	No	Exitus
3	Covered Metalic	100	13	No	No	No	Alive
4	Covered Metalic	100	90	No	No	No	Alive
5	Covered Metalic	100	No-operated	No	No	No	Alive
6	Covered Metalic	80	No-operated	No	No	No	Alive
7	Covered Metalic	210	19	No	No	No	Exitus
8	Covered Metalic	210	13	No	No	No	Alive
9	Covered Metalic	210	10	No	No	No	Alive
10	Covered Metalic	210	17	No	No	No	Alive
11	Non-Covered Methalic	120	No-operated	No	No	No	Alive
12	Non-Covered Methalic	160	No-operated	No	No	No	Alive
13	Non-Covered Methalic	160	No-operated	No	No	No	Alive
14	Non-Covered Methalic	160	No-operated	No	No	No	Alive
15	Non-Covered Methalic	160	No-operated	No	No	No	Alive
16	Non-Covered Methalic	90	No-operated	Yes	Yes **	No	Exitus
17	Non-Covered Methalic	70	No-operated	Yes	Yes **	No	Exitus
18	Non-Covered Methalic	160	No-operated	No	No	No	Alive

*: four session **: three session

RESULTS

The medical records of a total of 18 patients aged between 19 and 89 years (mean±SD: 53.5±20.3 years), of whom 8 (44.40%) were males and 10 (55.6%) were females, were retrospectively reviewed. The age ranged from 21 to 71 years (mean±SD: 50.8±16.4 years) for male patients and 19 to 89 years (mean±SD: 55.7±23.7 years) for female patients. There was a significant difference between the mean ages of both sexes ($p<0.001$).

A favorable outcome was achieved in 15 (83.3%) of 18 patients undergoing a single session of SEMS implantation procedures, whereas 3 patients needed more than two sessions of SEMS implantation procedures. Temporary SEMS implantation was performed to eliminate complications in 8 (44.4%) patients, whereas permanent SEMS implantation was performed in 10 (55.6%) patients with advanced esophageal or gastric cancer.

In more than 70% of patients undergoing SEMS implantation, the primary underlying pathologies were esophageal cancer (n=4) and gastric cancer (n=9). Malignant esophageal strictures restricting food intake and causing severe chest pain were detected in both patients with advanced esophageal cancer (Figure 1). Permanent SEMSs were implanted in all patients. Three of the patients were lost to metastatic cancer despite total clinical and technical success. Among the three patients who underwent total gastrectomy with Roux-en-Y esophagojejunostomy because of gastric cancer, two developed anastomosis leak and one anastomosis stricture after the operation. All three patients underwent SEMS implantation. In

two of the patients, anastomosis leak and stricture were completely eliminated after stenting, and stents were retrieved endoscopically in a short time. Despite this, a total of four stenting sessions were needed in a 37-year-old patient. Despite the elimination of esophagojejunostomy anastomosis leak after the first stenting procedure in that patient, a resistant anastomotic stricture developed approximately 2 months later. To solve the stricture issue, a total of four sessions of bougie dilatation and submucosal steroid injection were performed at a 15-day interval. Persistence of symptoms despite these measures necessitated a second stenting procedure in that patient, who developed severe resistant chest pain leading to endoscopic stent retrieval 15 days after the second stenting procedure. A third stent was implanted because of recurrent stricture-related complaints during follow-up. However, the stent migrated distally 2 days after the procedure (Figure 2). The migrated stent was spontaneously eliminated without a need for any additional intervention. The patient underwent a fourth stenting procedure 1 month later because of persisting stricture-related complaints. No stricture was detected at a 6-month follow-up.

In more than 27% of patients, SEMSs were implanted in the stomach (n=4) and esophagus (n=1) for benign conditions. Of these patients, four underwent the procedure for stapler line leak after laparoscopic sleeve gastrectomy for morbid obesity, whereas the other patient received a stent for esophagopleural fistula secondary to pulmonary tuberculosis. A 19-year-old woman with mental retardation and multiple comorbidities, who underwent sleeve gastrectomy, developed an abscess in the vicinity of the stomach following anastomosis leak. The complication was first intervened with percutaneous drainage but her metabolic condition and infectious parameters did not recover; therefore, an SEMS was implanted. The patient was lost to multiple organ failure 2 days after the stenting procedure. A 36-year-old woman without previously known pulmonary tuberculosis had been diagnosed with esophagopleural fistula at another center. At the same institution, lung tuberculosis had been also diagnosed, and anti-tuberculous treatment had been started. The patient received an esophageal stent in a single session. Her stent was retrieved endoscopically 40 days later when cessation of leak was radiologically confirmed (Figure 3). Tables 1 and 2 show the demographic, clinical, and follow-up data of all patients included in the present study.

DISCUSSION

Endoscopic stents have been widely used for the treatment of many benign and malignant conditions of the gastrointestinal tract, which formerly could be treated solely by surgical therapy. Stents have also been used to replace invasive procedures, such as relaparotomy, in the management of many postoperative complications (12, 13, 15). Widespread use of stents in many centers worldwide and their favorable outcomes have led to the use of these devices by many surgeons in a courageous manner. This paved the way for progressively increasing diversity of stenting indications and stent quality. It is now possible to access many stents of variable properties and types in many countries worldwide. No significant differences exist between the technical and clinical success rates of covered and uncovered stent applications, both of which are currently widely used (12). Uncovered stents prevent obstructive jaundice when used for the palliation of pathologies with special location (such as those located where the common bile duct opens into the duodenum) that cause strictures in the gastrointestinal system (13). Covered stents have the disadvantage of having a greater tendency to migrate, whereas uncovered stents have a greater tendency of being obstructed. In the present, in addition to the management of benign esophageal strictures, leaks, and perforations, stents are used for the palliative treatment of malignant dysphagia and gastric outlet obstruction, esophageal leaks following surgery, and/or stapler line leaks following sleeve gastrectomy. The success rate ranges between 72% and 100% (12, 16, 17). Among the cases presented in the present study, 7 received covered stents because of leak (n=6) or fistula (n=1), although the success of stenting could not be determined because one patient died on the second day of stenting.

Self-expandable metallic stent ensures a much lower mortality and morbidity than surgical procedures, in the form of either primary operations or relaparotomy procedures. In conclusion, SEMS implantation is a highly effective treatment for eliminating a variety of complications following surgery, starting oral feeding at an early period, shortening the duration of hospital stay, eliminating/palliating symptoms such as pain, preventing aspiration-associated infections, reducing overall cost, preventing recurrent laparotomies, and improving the quality of life (17-19). Although we had experience in biliary stent implantation for a long time, we performed first stent implantation in the gastrointestinal tract 18 months ago. We employed the stenting procedure for palliative treatment of dysphagia in two of our patients and for definitive treatment in the remaining patients.

Literature reports have stated mild, moderate, or severe chest pain as the most common complicationsof stent implantation in the upper gastrointestinal tract (12%–30%) (12, 13, 15, 20). Pain results from an increased pain sensitivity in the upper part of the esophagus and from mucosal erosion caused by reflux as a result of surgeries in the lower part. Fortunately, pain usually subsides after the administration of medication, such as analgesics and antireflux drugs. The other complications after stenting include bleeding, restenosis (0%–6%), stent folding, early or late migration (0%–58%), pneumomediastinum, tracheoesophageal fistula (0%–10%), perforation (0%–4.9%), and stent obstruction by food materials (8, 9, 17, 20). These complications are usually eliminated by medications or circumstance-specific treatments, although surgical therapy is also seldom required.One of our patients with gastric cancer developed anastomosis leak, resistant stricture, chest pain, and stent migration. Occurrence of these four complications in a single patient at different time points was considered bad luck. The patient received a total of four stents at four different times.

Four of 18 patients presented here died. Three patients who presented with advanced esophageal cancer underwent stenting for palliative purposes. However, two patients were extremely cachectic and were lost to metabolic complications of the tumor, although the patient's tolerance to oral food was well. Hence, mortality of these patients was not directly related to stenting. The other patient was lost 2 days after stenting because of leak after sleeve gastrectomy. A medical approach followed by interventional radiological approaches was selected

for treating the patient's leak. The patient was consulted and stented by us after the emergence of multiple organ failure. However, the patient was lost despite stenting because the clinical condition became irreversible. We also consider the loss of the patient independent of the stenting procedure and believe that an early stenting attempt could have brought the leak under control. In summary, our experience obtained from both deceased patients and the remaining successful cases is that an early stenting procedure is significant in cases with accurate indications.

CONCLUSION

Endoscopic stenting procedure is characterized by high patient comfort and low morbidity and mortality rates and is employed for primary treatment and postoperative complication management of many benign and malignant disorders of the upper gastrointestinal tract.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kahramanmaraş Sütçü İmam University School of Medicine.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.E., M.S., S.A.; Design - A.E., O.E., N.Y.; Supervision - İ.T.K., E.B., A.E.; Resource - A.E.; Materials - A.E., O.E., N.Y.; Data Collection and/or Processing - A.E., O.E., N.Y.; Analysis and/or Interpretation - A.E., S.A.; Literature Search - A.E., S.A., N.Y.; Writing Manuscript -A.E.; Critical Reviews - İ.T.K., A.E., S.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 106-110
DOI: 10.5152/turkjsurg.2018.3735

Splenectomy proportions are still high in low-grade traumatic splenic injury

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ABSTRACT

Objective: The spleen is the most vulnerable organ in blunt abdominal trauma. Spleen-preserving treatments are non-operative management with or without splenic angioembolization, partial splenectomy, and splenorrhaphy. The aim of the present study was to determine the rate of SPTs and to evaluate the usefulness of Injury Severity Score after traumatic splenic injury.

Material and Methods: We searched our institution's database between May 2012 and December 2015. Patients' clinicopathological features, surgeon's title, type of treatment, admission and discharge dates, duration of surgery, intensive care unit requirement, and Glasgow Coma Scale were recorded.

Results: The mean age of patients was 33.36±11.58 years. Of the 33 patients, 26 (78.8%) were males, and 7 (21.2%) were females. Thirty (90.9%) had total splenectomy (TS), and 3 (9.1%) had spleen preserving treatment (2 Nonoperative management and 1 partial splenectomy). No fatal hemorrhage developed after nonoperative management. Exitus rates were 5/30 (15.1%) and 0/3 in the total splenectomy and spleen preserving treatment groups, respectively. Of the 18 hemodynamically stable patients, only 2 (11.1%) had spleen preserving treatment. Of the 19 patients with grade I–III splenic injury, only 3 (15.8%) had spleen preserving treatment. For academic and non-academic surgeons, spleen preserving treatment rates were 3/11 (27.3%) and 0/22 (0%), respectively ($p<0.05$). Injury severity score and mean arterial pressure, number of transfusions, control hematocrit, and GCS had statistically significant relationships.

Conclusions: Spleen preserving treatment proportions were low after traumatic splenic injury. Following trauma, guidelines will not only improve spleen preservation rates but also improve the overall health status of the patients and it will also prevent complications of splenectomy.

Keywords: Splenectomy, surgery, emergency, spleen-preserving treatment, trauma

Cite this paper as:
Belli AK, Özcan Ö, Dinç Elibol F, Yazkan C, Dönmez C, Acar E, Nazlı O. Splenectomy proportions are still high in low-grade traumatic splenic injury. Turk J Surg 2018; 34: 106-110.

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This study was presented at the "20th National Surgical Congress", 13-17 April 2016, Antalya, Turkey.

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Received: 25.10.2016
Accepted: 18.05.2017
Available Online Date: 30.04.2018

Available online at
www.turkjsurg.com

INTRODUCTION

The spleen is the most vulnerable organ in blunt abdominal trauma owing to its location and vascularization. Splenectomy is the only treatment for all splenic injuries before 1960 (1). However, spleen-preserving treatments (SPTs) including non-operative management (NOM) with or without splenic angioembolization (SAE), partial splenectomy, and splenorrhaphy have been gradually implemented in time.

The spleen has several critical functions according to its histological parts including the red pulp or white pulp. In the red pulp, it filters and removes senescent erythrocytes in the circulation and recycles iron for the production of new erythrocytes. In the white pulp, it functions as a secondary lymphoid organ and generates both humoral and cellular immune responses. Moreover, 30% of the total thrombocytes are sequestered in the spleen. After splenectomy, cytoplasmic inclusions, including Heinz or Howell–Jolly bodies, occur in the erythrocytes, and the number of granulocytes and thrombocytes start to increase. Complications of splenectomy include atelectasis, pancreatitis, postoperative hemorrhage, thromboembolism, portal vein thrombosis, and fulminant bacteremia (2).

The aim of the present study was to determine the rate of SPTs in our institution, which factors are effective on the treatment choice, and to evaluate the usefulness of Injury Severity Score (ISS) after traumatic splenic injury.

MATERIAL AND METHODS

The study was performed in accordance with the Declaration of Helsinki.

Patient selection

We searched our institution's database between May 2012 and December 2015 to identify patients who had total or partial splenectomy due to trauma. Data were collected from the institution's archive. Patients who had splenectomy due to non-traumatic causes were excluded from the study.

Data collection

We started to search our database from May 2012 because our electronic health record system was set up to the current database system. Patient name, gender, date of surgery, surgeon's title, academic or non-academic, type of treatment (NOM, partial splenectomy, or total splenectomy (TS)), admission and discharge date, duration of surgery, referral status from outside hospitals, intensive care unit (ICU) requirement, Glasgow Coma Scale (GCS), number of transfusions such as erythrocyte suspension (ES) and fresh frozen plasma (FFP), and injuries other than the spleen were recorded in an electronic database system.

Transfusions given between the induction of anesthesia and finalization of surgical operation were called perioperative transfusions, and the number of transfusions given during hospital stay was called total number of transfusions.

Table 1. Clinical and pathological features of the patients according to treatment choice

	Total splenectomy (n=30) Mean±SD or median (min–max)	Spleen-preserving treatment (n=3) (NOM: 2, partial splenectomy: 1) Mean±SD or median (min–max)
Mean age (year)	33.9±11.6	28±10.8
Gender		
Male	24 (80%)	2 (66.7%)
Female	6 (20%)	1 (33.3%)
Surgeon's title		
Non-academic surgeon	22 (73.3%)	0 (0%)
Academic surgeon	8 (26.6%)	3 (100%)
Hemodynamic status		
Stable	16 (53.3%)	2 (66.7%)*
Unstable	14 (46.7%)	1 (33.3%)*
Grades of splenic injury		
I–III	19 (65.5%)	3 (100%)
IV–V	10 (34.5%)	0 (0%)
ICU status		
Required	15 (50%)	1 (33.3%)
Not required	15 (50%)	2 (66.7%)
Median ISS	21 (4–75)	17 (9–22)
Median GCS	15 (3–15)	15 (14–15)
Median duration of surgery (min)	100 (50–165)	40 (40–40)
Mean hospital stay (days)	7 (0–31)	6 (5–7)
Median total ES	3.36 (0–18)	1 (0–2)
Median perioperative ES	1.27 (0–10)	0 (0–0)
Mean total FFP	1.77±1.87	1±1.73
Median perioperative FFP	0.46 (0–4)	0 (0–0)

*Hemodynamically stable patients were treated with NOM, and unstable patients were treated with partial splenectomy
SD: standard deviation; ICU: intensive care unit; ES: erythrocyte suspension; FFP: fresh frozen plasma; ISS: Injury Severity Score; GCS: Glasgow Coma Scale; NOM: non-operative management

We defined an academic surgeon according to the following criteria: a surgeon who works in a teaching hospital and giving lectures to medical students and/or residents and who supposedly follow current treatment guidelines. On the other hand, a non-academic surgeon was defined as a general surgeon who has no teaching responsibility.

Calculation of ISS

We searched all injuries other than the spleen from the patient files and determined the organ injury scales (Abbreviated Injury Scale scores) and ISS calculated for each patient according to Baker et al. (3).

Evaluation of hemodynamic stability

We calculated mean arterial pressures (MAPs) from the initial and control systolic and diastolic blood pressures (SBP and DBP) using the following formula: MAP = 1/3×SBP+2/3 DBP). The control BP was measured after administering 500 to 1500 cc intravenous crystalloid infusion. We accepted operating room BP if there was no control BP in the emergency setting. Difference between the initial and control hemoglobin (Hb) and hematocrit (Hct) levels was calculated using the following formula: ((initial Hb−control Hb)/initial Hb×100) and ((initial Hct−control Hct)/initial Hct×100). Hemodynamic instability criteria were as follows: (1) a MAP level <65 mm Hg in the control BP and (2) an Hb or Hct difference percentage >20.

Grading of splenic injury

Our radiologist re-evaluated all patients' abdominal computed tomography (CT) scans according to the American Association for the Surgery of Trauma (AAST) grading system. Of the 33 patients, 29 had appropriate CT images for AAST grading. We also checked the pathology reports for the remaining patients for grading. One patient had no grading data available.

Our staff

Two professors, three assistant professors, and eight general surgeons were working in the department of general surgery while conducting this research.

Statistical analysis

We performed all statistical analysis after obtaining consultation from the Department of Biostatistics. Since SPTs are gold standards of treatment for grade I–II and recommended for grade III splenic injury and TS is recommended for grade IV–V injury according to the trauma guidelines, we categorized patients into grade I–III and grade IV–V to perform a better statistical analysis for the grades. We compared two categorical data with either Pearson chi-square or Fisher's exact test. To compare a categorical and a scale data, we used independent samples t or Mann–Whitney U tests. For the scale data, we used Pearson correlation test.

RESULTS

Of the 33 patients who had traumatic splenic injury, 26 (78.8%) were males, and 7 (21.2%) were females. The mean age of patients was 33.36±11.58 years (ranging from 7 to 59 years). Of the 33 patients, 30 (90.9%) had TS, and 3 (9.1%) had SPT (2 NOM and 1 partial splenectomy). No fatal hemorrhage developed during the follow-up of the patients treated with NOM. Exitus rates were 5/30 (15.1%) and 0/3 in the TS and SPT, respectively. Eighteen (54.5%) were hemodynamically stable, and 15 (45.5%) were unstable. Of the 18 hemodynamically

Table 2. Clinical features of the patients with splenic injury according to academic vs non-academic surgeons

Clinical features of the patients	Academic surgeon (n=11)	Non-academic surgeon (n=22)	p
Mean age (year)	30.6±12.6	34.7±11.08	0.77
Gender			
Male	8 (72.7%)	18 (81.8%)	0.66
Female	3 (27.3%)	4 (18.2%)	
Grades of splenic injury			
I–III	8 (72.7%)	14 (63.6%)	1
IV–V	3 (27.3%)	7 (31.8%)	
Hemodynamic status			
Stable	5 (54.5%)	13 (59.1%)*	0.48
Unstable	6 (45.5%)	9 (40.9%)*	
Median ISS	22 (4–75)	17 (4–75)	0.3
ICU status			
Required	6 (54.5%)	10 (47.6%)	0.71
Not required	5 (45.5%)	11 (52.4%)	
Median GCS	14 (3–15)	15 (12–15)	0.03
Median duration of surgery (min)	90 (40–120)	100 (50–165)	0.68
Median duration of hospital stay (days)	5 (0–27)	7 (0–31)	0.32
Median no. of consultations	4.5 (1–7)	3 (1–7)	0.23
Median total ES (packs)	3 (0–18)	3 (0–9)	0.89
Median perioperative ES (packs)	2 (0–10)	1 (0–5)	0.62
Mean total FFP (packs)	2±1.55	1.55±1.99	0.51
Median perioperative FFP (packs)	0 (0–4)	0 (0–3)	0.78
Treatment type			
SPT	3 (27.3%)	0 (0%)	0.03
Total splenectomy	8 (72.7%)	22 (100%)	

ISS: Injury Severity Score; ICU: intensive care unit; GCS: Glasgow Coma Scale; ES: erythrocyte suspension; FFP: fresh frozen plasma; SPT: spleen-preserving treatment

Table 3. Clinical features of the patients according to hemodynamic status

	Stable	Unstable	p
Mean age (year)	33.6±10.4	33.06±13.2	0.89
Mean initial MAP	77.25±12.2	72.22±15.1	0.31
Median initial fluid replacement	1000 (500–3000)	1000 (500–3000)	0.63
Mean control MAP	85.38±15.37	71±19.4	0.04
Mean Hct change %	−0.44±26.3	27.4±15.2	0.02
Median total ES (packs)	2 (0–9)	4 (0–18)	0.08
Mean total FFP (packs)	1.16±1.65	2.3±1.9	0.07
Median perioperative ES (packs)	1 (0–5)	1 (0–10)	0.91
Median perioperative FFP (packs)	0 (0–3)	0 (0–4)	0.21
Median duration of surgery (min)	90 (50–165)	120 (40–120)	0.5
Mean ISS	15.28±8.28	39.33±28.1	0.08
Mean hospital stay (days)	9.94±7.9	5.86±5.08	0.96
Median GCS	15 (8–15)	15 (3–15)	0.63

MAP: mean arterial pressure; Hct: hematocrit; ES: erythrocyte suspension; FFP: fresh frozen plasma; ISS: Injury Severity Score; GCS: Glasgow Coma Scale

Table 4. Statistically significant correlations between ISS and other clinical factors

Variables		p	Correlation coefficient (r)
ISS	Initial SBP	0.007	−0.46
	Control SBP	0.02	−0.51
	Initial MAP	0.02	−0.4
	Control MAP	0.03	−0.37
	Control Hct	0.04	−0.37
	Perioperative ES	0.04	0.36
	Perioperative FFP	0.04	0.36
	Total FFP	0.007	0.46
	GCS	0.001	−0.57

SBP: systolic blood pressure; MAP: mean arterial pressure; Hct: hematocrit; ES: erythrocyte suspension; FFP: fresh frozen plasma; ISS: Injury Severity Score; GCS: Glasgow Coma Scale

stable patients, only 2 (11.1%) had SPT. Thirty-two out of the 33 patients' information were available for grading; 6 (18.8%) had grade I, 2 (6.3%) had grade II, 14 (43.8%) had grade III, 3 (9.4%) had grade IV, and 7 (21.9%) had grade V splenic injury. Of the 22 patients with grade I–III splenic injury, only 3 (15.8%) had SPT. Of the 18 hemodynamically stable patients, only 2 (11.1%) had SPT. The mean ISSs were 15.28±8.28 and 39.33 ± 28.1 (p>0.05) for hemodynamically stable and unstable patients, respectively. Sixteen (48.5%) patients needed ICU postoperatively. Regarding the surgeon's title, there were three academic vs six non-academic surgeons (Tables 1-3).

Patients' clinical features according to academic and non-academic surgeons were the following: mean ages were 30.6±12.6 years and 34.7±11.08 years (p>0.05), grade I–III/IV–V proportions were 8/3 and 14/7 (p>0.05), hemodynamic stability/instability proportions were 5/6 and 13/9 (p>0.05), ICU requirements were 6 (54.5%) and 10 (47.6%) (p>0.05), median ISSs were 22 (4–75) and 17 (4–75) (p>0.05), median GCSs were 14 (3–15) and 15 (12–15) (p<0.05), and SPTs were 3 (27.3%) and 0 (0%) (p<0.05), respectively (Table 2).

ISS was negatively correlated with initial SBP (p: 0.007, r: −0.46), control SBP (p: 0.02, r: −0.51), initial MAP (p: 0.02, r: −0.4), control MAP (p: 0.03, r: −0.37), control Hct (p: 0.04, r: −0.37), and GCS (p: 0.001, r: −0.57); positively correlated with perioperative ES (p: 0.04, r: 0.36) and perioperative FFP (p: 0.04, r: 0.36) (Table 4).

DISCUSSION

Non-operative treatments with or without SAE, partial splenectomy, and splenorrhaphy are considered as SPTs. The advantages of spleen preservation are maintaining splenic function, avoiding post-splenectomy sepsis, and preventing thrombosis or laparotomy complications (4). Non-operative treatment was first used in pediatric splenic trauma in 1968 and is currently the gold standard of treatment in grade I–II splenic injury (1, 4, 5). The most important complication of NOM is delayed fatal hemorrhage; however, no delayed hemorrhage developed during the follow-up of our NOM patients who had grade III splenic injuries (6).

Jeremitsky et al. (7) investigated NOM success rates in 15.732 patients presenting with blunt splenic injury and reported that the overall splenic salvage rate is 81%, and the NOM success rate is 95% after 5 h of arrival. Dehli et al. (8) evaluated the success rate of SAE with NOM and reported that this combination decreases the rate of splenectomy. Nevertheless, Olthoff et al. (9) corrected the confounding factors using a propensity score while evaluating the success rate of SAE and found no significant difference between the patients who were observed and who had SAE.

The mortality rate of NOM for patients with grade I–II injury was found to be 0%. For grade III injuries, the mortality rate of NOM was found to be closer to operative managements. For grade IV–V patients, the NOM mortality rate was found to be higher than operative management (6, 10, 11). Since there was no contrast extravasation in abdominal CT images in grade III splenic injury and it is recommended by the guidelines, we tried to perform NOM in this group of patients. Thus, we categorized patients into grades I–III and IV–V, as mild and severe splenic injuries, to perform a better statistical analysis. In total, 3 patients with grade III splenic injury were treated with SPTs, with 2 NOM and 1 partial splenectomy, and all of them recovered with no complications in our study.

Several studies in Turkey reported spleen preservation rates ranging from 11% to 66% after a traumatic splenic injury (12-15). Koksal et al. (11) reported that the NOM rate for traumatic splenic injury is 12.2% between the years 1994 and 1997 in their institution and increases to 76.9% between the years 1998 and 2000 with a 100% NOM success rate. Arikan et al. (13) reported that traumatic splenic injuries are treated 89% with TS, 7% with splenorrhaphy, and 4% with partial splenectomy between the years 1992 and 1998 in their institution. Moreover, Yanar et al. (14) investigated the effective factors on NOM success rate and stated that the initial lactate level, solid viscus score, transfusion requirement, fluid replacement, and Hct change are significant factors. Furthermore, Topaloglu et al. (15) reported that the ratio of complications, including wound infection, lung infection, pneumothorax, urinary infection, and re-laparotomy, after a traumatic splenic injury is 18.06%.

Factors that influence the treatment choice after traumatic splenic injury have not been identified in the literature. One study from Olthof et al. (16) reported that SAE and surgery rates vary in five different academic hospitals; however, no effective factor was identified in the treatment choice. We found in our study that academic surgeons performed more SPT than non-academic surgeons even if the proportions were still low, 27% vs 0%. This relationship may be due to the fact that academic surgeons follow trauma guidelines better, take more surgical risks in their hospital settings, or are younger surgeons than non-academic surgeons. Academic surgeons' responsibility for resident and medical student training may lead them to perform contemporary procedures.

University hospitals, training and research hospitals, community hospitals, private hospitals, newly established affiliated hospitals, and union of university and community hospitals are types of hospitals in Turkey. Some institutions have been leading in modern treatment methods in Turkey such as university and training and research hospitals. However, to our knowledge, there is no study that compared the NOM rates for splenic injuries among these institutions, and there may be different rates of NOM among these institutions. Nevertheless, SPT proportion for patients who had low-grade splenic injury or patients who were hemodynamically stable is still very low and needs to be improved to be consistent with trauma guidelines. Moreover, our study is a unique study that investigated the factors affecting SPTs after traumatic splenic injury and may give rise to further investigations in this topic.

Furthermore, we also investigated the importance of ISS in traumatic splenic injury and found that it was significantly correlated with the initial and control SBPs and MAPs, number perioperative ES and FFP, total FFP, control Hct, and GCS. Therefore, it appears that calculating ISS for patients with trauma in an emergency room may assist physicians to determine the prognosis of the patient, required number of transfusions, or even the need for ICU requirement.

CONCLUSION

We found in our study that SPT proportions were still very low in traumatic splenic injury. This management is inconsistent with trauma guidelines. Surgeons should be more careful about following trauma guidelines to improve the overall health status of the patients and to prevent complications of splenectomy.

Ethics Committee Approval: The 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.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.K.B.; Design - A.K.B.; Supervision - A.K.B.; Resource - A.K.B., Ö.Ö., C.D., O.N.; Materials - A.K.B., Ö.Ö., C.D., O.N.; Data Collection and/or Processing - A.K.B., F.D.E., C.Y., E.A.; Analysis and/or Interpretation - A.K.B.; Literature Search - A.K.B, C.Y.; Writing Manuscript - A.K.B.; Critical Reviews - A.K.B., Ö.Ö., O.N.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 111-116
DOI: 10.5152/turkjsurg.2018.3771

Original Article

Effect of sildenafil citrate on the liver structure and function in obstructive jaundice: An experimental study

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ABSTRACT

Objective: We aimed to investigate the effect of 10 mg/kg sildenafil on the structure and function of the liver in a rat model of obstructive jaundice.

Material and Methods: Sixty-two male Wistar albino rats were distributed into six different groups. Obstructive jaundice was performed by legating the common bile duct. 10 mg/kg sildenafil citrate in drinking water was delivered orally after the operation before sacrificing them. Rats were sacrificed either after 10 or 28 days according to the study design. The blood and tissue samples from the liver were obtained to perform a biochemical and histopathological analysis to study functional and structural changes in the liver.

Results: At the 10th day, there was no difference between the sildenafil-treated and control groups with regard to the aspartate aminotransferase and alanine aminotransferase levels ($p=0.423$, $p=0.661$). The alkaline phosphatase total bilirubin levels among the groups were statistically different ($p<0.001$). At the 28th day, liver function tests except alanine aminotransferase showed significant differences among the groups ($p<0.001$). Liver function tests did not changed significantly between the 10th and 28th day in sildenafil-treated rats ($p>0.05$). Significant differences were observed among the groups with regard to cholestasis, fibrosis, inflammation, and necrosis ($p<0.001$). However, edema increased in the sildenafil-treated group ($p<0.001$). On the 28th day, the severity of structural changes in the liver after obstructive jaundice, except edema, reduced significantly ($p<0.001$). The sildenafil-treated groups at different time points didn't show any statistical difference in histopathological changes ($p>0.05$).

Conclusion: Oral administration of 10 mg/kg sildenafil citrate dramatically reverses the biochemical and histopathological liver changes induced by obstructive jaundice in rats.

Keywords: Sildenafil citrate, liver, obstructive jaundice, rats

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Cite this paper as:
Şimşek T, Ersoy ÖF, Özsoy Z, Yenidoğan E, Kayaoğlu HA, Özkan N, et al. Effect of sildenafil citrate on the liver structure and function in obstructive jaundice: An experimental study. Turk J Surg 2018; 34: 111-116.

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This study was presented at the "XVI. Annual Meeting of the European Society", 22–24 November, 2012, İstanbul, Turkey.

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Received: 21.11.2016
Accepted: 18.05.2017

INTRODUCTION

Obstructive jaundice develops as a result of a bile obstruction in the intrahepatic and/or extrahepatic biliary tract. The obstruction occurs somewhere between the bile production in the liver and its secretion in the gastrointestinal system (1). Depending on the etiology, an obstruction might be partial, or in some cases, a complete obstruction can occur. Clinical findings occurring with obstructive jaundice may be reversible with an early diagnosis and therapy when the cause of obstruction is removed. However, in some cases, when the cause of obstruction cannot be removed, or when the obstruction takes a longer time to clear, permanent functional and histopathologic changes can occur. The functional and structural changes that occur in the liver as a consequence of obstructive jaundice could return to normal after only days or weeks following an internal or external drainage process (2). For this reason, to minimize the development of liver injury in obstructive jaundice, several agents and methods have been and are still being investigated (3-7).

Phosphodiesterase-5 (PDE-5) enzyme inhibitors have different impacts on hemodynamic parameters in the liver (8). Sildenafil citrate is also a PDE-5 inhibitor and is often used for erectile dysfunction (8). Sildenafil causes the c-GMP levels to increase by inactivating PDEs that metabolize c-GMP. Furthermore, c-GMP is an intracellular mediator of the nitric oxide (NO) pathway and causes an increase in NO synthesis. NO causes relaxation of the vascular smooth muscle structure, vasodilatation, increases in blood flow, inhibition of platelet aggregation, and inhibition of both platelet aggregation and microcirculation (9). Under physiological conditions, NO plays an important role in the liver's microvascular blood flow (10).

In this study, we aimed to investigate the impacts of daily oral sildenafil (10 mg/kg) on functional and structural liver changes at 10 and 28 days of an experimental obstructive jaundice model in rats.

MATERIAL AND METHODS

Procedure and Evaluation

This study was approved by the Ethics Committee of Gaziosmanpasa University Medical Faculty. Rats were obtained from the Gaziosmanpasa University Experimental Research Center. All animals received humane care in accordance with local laboratory animal research regulations. Sixty-two male Wistar albino rats, weigh-

ing 250 to 300 g, were randomly allocated into six groups (Sham 10; Sham 28; Control 10; Control 28; Sildenafil 10; and Sildenafil 28). All operative processes and follow-up treatments were held at Gaziosmanpasa University Animal Studies Research Center. Rats were housed in wire cages with free access to food and water under standard laboratory conditions (room temperature: 23 °C; 12-hour light–dark cycles). They were not fed for 12 hours before the operation, but they had free access to water.

Surgery and Experimental Protocol

Before the operative process, anesthesia was induced by an intraperitoneal injection of ketamine hydrochloride (75 mg/kg; Ketalar, 500 mg flacon; Pfizer, Istanbul, Turkey) and xylazine hydrochloride (10 mg/kg; Rompun 2% flacon; Bayer, Istanbul, Turkey). After skin preparation, a midline laparotomy of 2–3 cm was made. The duodenum was found by following the stomach and pylorus. Through a slightly forward and downward traction of the duodenum, the common bile duct extending from the liver hilum to the duodenum was seen. Holding the fatty tissue with a thin hemostat, the common bile duct was released (11).

Group 1 (Sham 10): The rats in this group underwent only the common bile duct exploration, and then the process was ended. The rats were sacrificed on the 10th day.

Group 2 (Sham 28): The rats in this group underwent only the common bile duct exploration, and then the process was ended. The rats were sacrificed on the 28th day.

Group 3 (Control 10): The rats in this group underwent a mechanical obstructive jaundice model, and then the process was ended. The rats were sacrificed on the 10th day.

Group 4 (Control 28): The rats in this group underwent a mechanical obstructive jaundice model, and then the process was ended. The rats were sacrificed on the 28th day.

Group 5 (Sildenafil 10): The rats in this group underwent a mechanical obstructive jaundice model, and then the process was ended. After the procedure, 10 mg/kg/day of sildenafil was given orally until the time of sacrifice. The rats were sacrificed on the 10th day.

Group 6 (Sildenafil 28): The rats in this group underwent a mechanical obstructive jaundice model, and then the process was ended. After the procedure, 10 mg/kg/day of sildenafil was given orally until the time of sacrifice. The rats were sacrificed on the 28th day.

Experimental obstructive jaundice was induced by a knot tied on the common bile duct with 4/0 silk sutures and transected so as to prevent recanalization. The fascia and skin were closed by 4/0 monofilament polypropylene (Prolene, Ethicon) running sutures. All animals were resuscitated by a subcutaneous injection of saline (8–10 mL/kg) to the dorsal area.

Drug Application

The drug was completely crushed and mixed with 2–3 ml of drinking water. Then it was thoroughly mixed until it became a homogenous suspension. Using a gavage injector, the solution was completely administered orally. Starting from the day of the operation until the rats were sacrificed, sildenafil citrate (Vıagra, Pfizer; Istanbul, Turkey) was given in a 10 mg/kg dose by gavage every day at the same hour.

Sacrifice and Collecting the Blood and Tissue Samples

The rats in the sham, control, and sildenafil group were sacrificed on the 10th (Sham 10, Control 10 and Sildenafil 10) or 28th day (Sham 28, Control 28 and Sildenafil 28) according to the study design. The blood and tissue samples were collected for biochemical analysis of liver functions and for histopathological evaluation of liver structural changes. Sacrifice was performed in accordance with laboratory conditions. Before the procedure, the rats were anesthetized with 30 mg/kg hydrochloride and 5 mg/kg xylazine. After the intracardiac blood sampling, a laparotomy through the previous incision was made, and a total hepatectomy was performed.

Biochemical Analyses of Liver Functions

The blood samples were centrifuged for 5 minutes at 2,000 rpm, and the plasma was separated. Aspartate aminotransferase (AST; U/L), alanine aminotransferase (ALT; U/L), alkaline phosphatase (ALP; U/L) and total and direct bilirubin (TBIL and DBIL, respectively; mg/dl) levels were measured with the enzyme-linked immunosorbent assay.

Histopathological Evaluation of Liver Structural Changes

The histological evaluations of the specimens were performed by the same blinded pathologist. The hepatic tissue specimens were fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin for histopathological evaluation. Histopathological examinations of the prepared samples were done by light microscopy. In the examination of the liver tissue samples, ductal proliferation, periductal edema, cholestasis, portal and periductal inflammation, and the presence of necrosis were examined. The extent of histopathological changes in the liver tissue was graded by using a 4-point scoring system (0, none; 1, mild; 2, moderate; and 3, severe).

Statistical Analysis

All data are presented as the mean ± standard deviation. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 13.0 (SPSS Inc.; Chicago, IL, USA). Statistical evaluation of numeric variables was performed by a one-way analysis of variance, followed by a Tukey's post hoc test. Non-numeric variables were evaluated with the χ^2 test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

No intraoperative or postoperative deaths occurred in the rats. We also did not observe any infective complications in either the control or experimental groups during the followup period.

Biochemical Measurements

Liver function tests after 10 and 28 days showed a significant difference between the sham group and other groups ($p<0.001$). Although there was a decrease in the AST, ALT, and DBIL levels of the groups treated with sildenafil when compared to the control groups, this difference was not statistically significant. For the ALP and TBIL levels, a significant difference was seen among all groups ($p<0.001$) (Figure 1). On the 28th day, there were significant differences in the AST, ALP, TBIL, and DBIL measurements between the sildenafil group and the

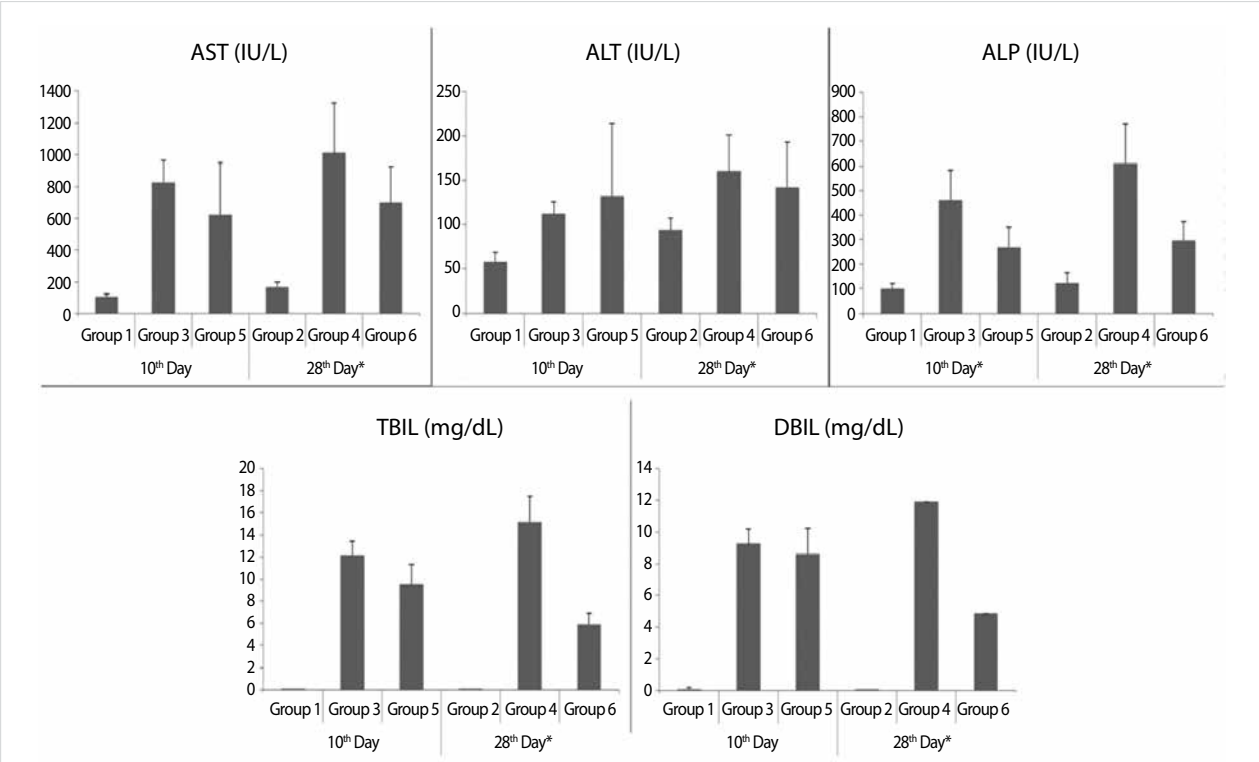

Figure 1. Results of Liver Function Tests
AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; TBIL: total bilirubin; DBIL: direct bilirubin
* Statistically significant (p<0.001)

control group (p<0.001). A decrease was also seen in ALT levels, but this was not significant (p=0.1) (Figure 1). On the 10th and 28th days, when the sildenafil groups were compared between each other in terms of liver function tests, no significant difference was seen (p>0.05).

Histopathological Evaluations

On the 10th and 28th days, a significant difference arising from the sham group was seen with regard to ductal proliferation (p<0.001). However, there was no significant difference between the control group and sildenafil group (p>0.05). On the 10th and 28th days, a significant difference regarding cholestasis, fibrosis, edema, inflammation, and necrosis were detected in all groups (p<0.001). In the sildenafil group, a significant decrease in cholestasis, fibrosis, inflammation, and necrosis levels were noticed (p<0.001). In this group, edema increased on the 10th day (p<0.001) and remained the same on the 28th day (p=0.112). On the 10th and 28th days, no significant differences were seen in terms of histopathological changes when the sildenafil groups were compared with each other (p>0.05). However, although there was no significant difference, an increase in the level of ductal proliferation, fibrosis, and necrosis, and a decrease in edema and inflammation were observed on the 28th day. There was no change in cholestasis levels. Histopathological changes in the liver induced by sildenafil citrate in rats are presented in Figure 2.

DISCUSSION

Obstructive jaundice is an area intensively studied both experimentally and clinically. However, despite new improvements in its treatment, it is still one of the most important surgical problems. Endotoxemia has a significant role in the pathophysiological changes that occur (12). Two factors are responsible for endotoxemia development. The first is the absence of an anti-endotoxin effect provided by bile salts in the digestive tract, and the absorption of endotoxins into the portal circulation. The second is the escape of endotoxins arising from the bowels into the systemic circulation due to the impairment of phagocytic functions of the hepatic Kupffer cells (13, 14). Emerging systemic endotoxemia activates an inflammatory response causing organ functions to deteriorate. Related to these changes, a clinical picture might develop with severe morbidity and mortality, and it may include conditions such as acute respiratory distress syndrome, renal failure, hepatorenal syndrome, several cardiovascular problems, and multiple organ failure (15). Thus, for these reasons, obstructive jaundice is extensively studied both experimentally and clinically. While in hepatocellular damage the increase in AST is more prominent, in obstructive jaundice, the increases in ALP, TBIL, and DBIL are at the forefront (16). In our study, the highest levels among the control groups in terms of liver function tests were observed remarkably on the 28th day. The reason for this is due to the damage of prolonged biliary retention on liver cells (17). In our study, the decrease in ALP and TBIL levels in liver function tests were significant in the group treated with sildenafil for 10 days. On the 28th day, a decrease in all liver function tests, except for ALT, was seen in all the sildenafil groups. This result shows that the long-term use of sildenafil is effective in recovery of liver function tests that decreased due to obstructive jaundice.

In obstructive jaundice, an increase in the biliary pressure due to the accumulation of bile salts occurs in the common bile duct. During the first week of the obstruction, edema, neutro-

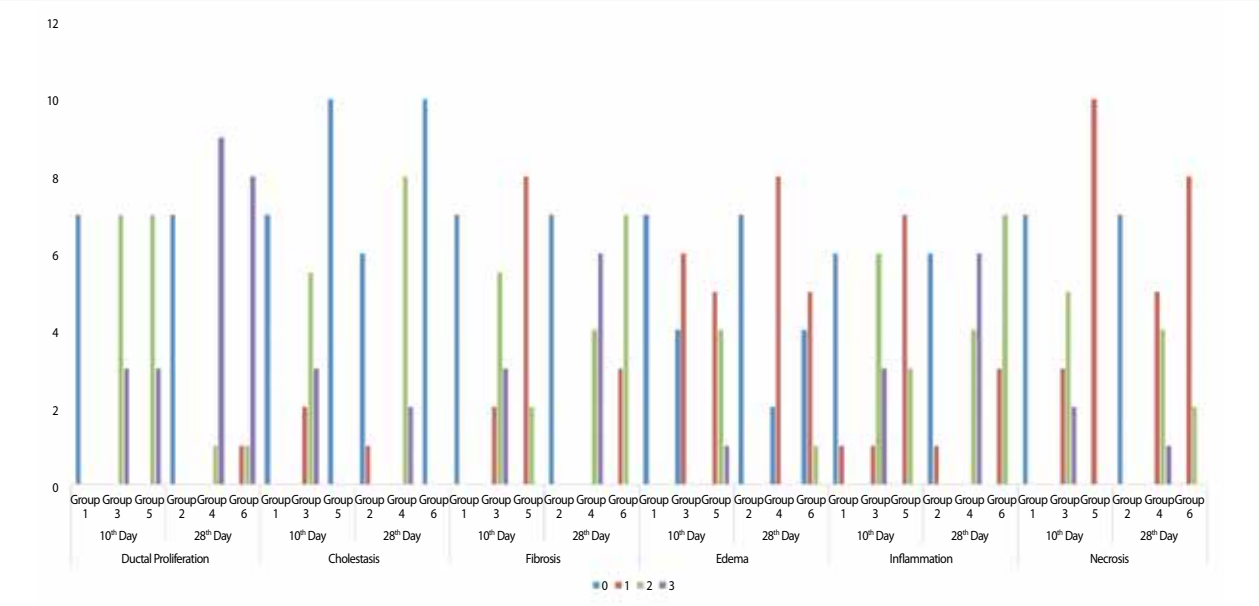

Figure 2. Histopathological Changes in the Liver Induced by Sildenafil Citrate in Rats
In the examination of liver tissue samples, ductal proliferation, periductal edema, cholestasis, portal and periductal inflammation, and the presence of necrosis were examined. The extent of histopathological changes in the liver tissue was graded by using a 4 point scoring system (0, none; 1, mild; 2, moderate; and 3, severe)
Significant differences were observed among the groups with regard to cholestasis, fibrosis, inflammation, and necrosis ($p<0.001$). However, edema increased in the sildenafil-treated group ($p<0.001$). At the 28th day, the severity of structural changes in the liver after obstructive jaundice, except edema, was reduced significantly ($p<0.001$)

phils, and lymphocytes might be seen in the portal area. Along with portal inflammation, bile duct proliferation is observed in the periportal area. If the obstruction continues, fibrosis and fibrous septa are noticed along periportal and periseptal areas, which are indicators of chronic cholestasis. Related to the increased collagen content, hepatic stricture occurs. The regenerative ability of the liver decreases, and fibrogenic activity increases. Fibrosis then replaces the normal liver structure. The causes of bile infarcts developed during the late period include a duct damage related to increased biliary pressure, the direct impact of bile components on hepatocytes, and the indirect impacts of bilirubin and bile acids in the blood. As the infarct develops, fibrotic and necrotic areas increase, and the tissue damage becomes permanent. Morphological changes continuing in the liver result in the occurrence of secondary biliary cirrhosis and regeneration nodules after months (17). In electron microscopic studies of the obstructive jaundice model, hepatocytes were observed to lose their secretory functions. It was found that mitochondria swelled, and serious deformities occurred. Additionally, due to the decrease in protein synthesis, gluconeogenesis and ketogenesis disorders of mitochondrial activity were found (18, 19). In our study, we found a significant decrease in many of the negative effects of delayed bile emptying in the early (10th day) and late (28th day) periods on liver tissue in the obstructive jaundiced rats treated with sildenafil. For instance, decreases in cholestasis, fibrosis, inflammation, and necrosis were observed in both time periods; however, edema was increased only in the early period.

The vasodilatation effect of sildenafil and PDE-5 inhibitors causes the activation of kinases through the release of endogenic mediators such as bradykinin and/or adenosine and subsequent NO synthesis. NO forms c-GMP by activating guanylate cyclase. C-GMP opens mitochondrial K-ATP channels by protein kinase G (PKG) activation. It is thought that, in cases when intracellular pH and ATP synthesis decrease, as with ischemia-reperfusion, the opening of these channels reactivates metabolic functions by stabilizing the intracellular acidic environment, and therefore, it might be effective in preventing damage. K-ATP channels are found not only in the heart, but also in all endothelial cells of the body.

NO exerts a positive impact on several stages of wound recovery due to its effects on angiogenesis and inflammation in the endothelium and epithelium. Kim et al. (20) showed that necrosis developing in ischemia-reperfusion damage of NO can be prevented by c-GMP and the guanylate cyclase–dependent kinase pathway. Gursoy et al. (21) researched the impact of sildenafil on wound recovery and showed that sildenafil makes a positive contribution by increasing the neovascularization and abdominal wall tensile force. Cakir et al. (22) stated that sildenafil had a histopathologically positive impact on colon anastomosis recovery. Sarifakioglu et al. (23) examined the effect of sildenafil citrate on the flap life and showed that it increased the length of flap life, a property they suggest comes from two sildenafil features. These features include the promotion of increased vasodilation and the prevention of potential vascular thromboses by affecting thrombosis aggregation. Tas et al. (24) showed that sildenafil increased new capillary formation as well as vasodilatation. Furthermore, Irkorucu et al. (25) found that sildenafil causes a decrease in mucosal damage.

As for the liver, sildenafil decreases vascular resistance by increasing the NO release and decreasing the portal pressure (26, 27). Colle et al. (28) examined the impact of sildenafil on rats with experimentally induced cirrhosis. They founded that intramesenteric and intravenous injections of sildenafil decreased the mean arterial blood pressure and increased the

mesenteric blood flow and portal venous pressure, depending on the dosage. In a different study, it was stated that no significant increase was observed in superior mesenteric artery blood flow in an experimental obstructive jaundice model when NO synthesis was prevented; subsequently, no significant recovery occurred in either liver functions or tissue histopathological changes (29). Li et al. (30) examined the impact of sildenafil in experimental liver damage in rats. They found that liver hypoxia and liver damage decreased due to the increase in smooth muscle relaxation caused by increased NO levels generated by sildenafil. At the end of this study, they concluded that sildenafil might prevent damage in post-ischemia hepatocytes by regulating oxygen consumption.

Although it is rare according to literature, in some studies, hepatotoxicity is reported to be caused by sildenafil. The sildenafil citrate was investigated in a study published in 2011, in terms of its histological effects on adult Wistar rats that were treated with sildenafil every day, for a period of 6 weeks (31). Regarding the histological results, the study reported a dilatation of the central vein of the liver with lysed red blood cells and a cytoarchitectural distortion of the organ. Increased levels of liver enzymes were also noted. It was suggested that a probable toxic effect of sildenafil might have affected the hematopoietic function of the liver to a great extent. The study conducted by Nna et al. (32) reports that as it is indicated in the increased serum concentration of liver enzymes and bilirubin, significant alteration in liver functions could occur following the chronic administration of sildenafil in adult Wistar rats; and only a poor reversal of hepatotoxicity was observed after the withdrawal of the sildenafil. Jarrar and Almansour. (33) reported that significant biochemical and structural alterations in the hepatic tissue that have potential effects on liver functions were observed as a result of subchronic exposure to sildenafil overdoses (e.g., hepatocytes nuclear alterations, necrosis, bile duct hyperplasia, inflammatory cells infiltration, hepatic vessels congestion). Even though a possible link between hepatotoxicity and the use of sildenafil is indicated in the related literature, the mechanism underlying liver toxicity still remains unknown. However, it should be considered that the manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure, and so it could be possible that some sildenafil-associated hepatotoxicity cases may have been totally missed, especially when sildenafil consumption is not declared, illicit, and/or unaware (i.e., in case of counterfeit herbal products for erectile dysfunction) (34-37). Normality values were noted in clinical condition and liver enzymes within 20 days after the withdrawal of sildenafil, which indicates a diagnosis of sildenafil-associated hepatotoxicity from unknown mechanisms (34).

There are some limitations to this study. First, based on the molecular mechanisms mentioned before, an increased NO synthesis might have led to the positive biochemical and histopathological effect of sildenafil on hepatocytes in obstructive jaundice in this study. However, this study did not research this issue. Second, obstructive jaundice has been reported to cause significant oxidative stress and inflammatory reaction in the liver. Although this study showed that inflammation, necrosis, and fibrosis reduced with treatment, its antioxidative effect was not assessed.

CONCLUSION

This study showed that the use of 10 mg/kg of sildenafil by an oral route for 10 and 28 days in an experimental obstructive jaundice model might amend the functional and structural liver changes occurring during biliary obstruction. In this model, the inflammation, necrosis, and fibrosis observed in the liver tissue during prolonged jaundice decreased significantly with sildenafil. We think that the effect of sildenafil on obstructive jaundice should be investigated in more detail both at the molecular level and with regard to its clinical use.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziosmanpaşa University School of Medicine.

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.S., O.F.E., N.O.; Design - T.S., O.F.E., Z.O., N.O.; Supervision - E.T., H.A.K.; Resource - T.S., O.F.E.; Materials - T.S., O.F.E., N.O., Z.O.; Data Collection and/or Processing - T.S., O.F.E., Z.O.; Analysis and/or Interpretation - T.S., O.F.E., Z.O.; Literature Search - T.S., Z.O.; Writing Manuscript - T.S., O.F.E., Z.O., E.Y.; Critical Reviews - Z.O., H.A.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 117-120
DOI: 10.5152/turkjsurg.2017.3867

Original Article

Management of huge and extraordinary metal-penetrating injuries to the hand

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ABSTRACT

Objective: Foreign-body and penetration injuries of the hand are common emergencies. Metallic foreign bodies are common among all foreign masses; however, the examination of huge bodies differs from that of other metallic masses. The purpose of this study was to clarify an algorithm for the management of the huge metallic masses via our therapeutic approaches for metal-penetrating injuries.

Material and Methods: Seven patients who had a huge, metallic object-penetration injury to their upper extremity were included in our study. Patients were classified according to the age, injury type, character of metallic body, injury zone, diagnostic methods, anesthesia type, and treatment received, and an algorithm to approach the management of foreign metallic bodies was clarified.

Results: The causes of injury were knitting hook, iron fence, mixer, and metal nail. Plain radiography was performed for all patients. Prophylactic tetanus was administered and urgent exploration in the operation room under tourniquet followed by foreign-body extraction through cutting and not pulling were conducted. No residue was retained.

Conclusion: Many patients referred to emergency services with foreign bodies. For diagnosis, the patient's history and a minimum of two-way radiograms are crucial. For treatment, we recommend surgical exploration under general anesthesia and tourniquet and extraction of the metallic body by cutting and not pulling without retaining any residual mass in the operation room.

Keywords: Foreign body, hand, mass, metal

INTRODUCTION

Foreign bodies and penetration injuries of the hand are common emergencies. These cases are crucial because of the possibility of neurovascular, skeletal, or soft tissue injuries; allergic reactions; migration; or delayed wound healing (1).

Metallic foreign bodies are common among all foreign masses; however, the examination of the huge bodies differs from that of other metallic masses. Also, huge metallic bodies may present as traumatic and reactive masses and can be a mechanical load for the hand or can cause hand disabilities. In addition, huge metallic bodies are challenging to remove due to a high risk associated with pulling the mass.

The purpose of this study was to clarify an approach for the management of the huge metallic masses via our therapeutic approaches for metal-penetrating injuries.

MATERIAL AND METHODS

Seven patients who had an extraordinary, metallic object-penetration injury between January 2012 and January 2015 were included in the study. All patients were admitted within 24 hours. The study was designed in accordance with the principles of Helsinki Declaration.

Metallic splinters and bullet penetration cases were excluded because these were not classified as huge objects. The criterion for an extraordinary object was being a visible penetrating mass. Patients admitted with residual foreign bodies, high-pressure injection injuries, and foreign bodies other than metal (such as wooden splints, glass, and mercury) injury were excluded from the study. If patients did not already have a foreign body in their hand, they were excluded from the study even if they were injured with a metal foreign body (such as needle stick or fishhook injuries).

Patients were retrospectively classified according to the age (<18, 18–65, or >65 years), injury type (industrial injury, home accident, or others), nature of the metallic body (knitting hook, iron fence, metal nail, mixer, or others), injury zone (finger, palm, or wrist), diagnostic methods (hand examination, X-ray, ultrasonography, magnetic resonance imaging, none, or combined), anesthesia type (local, regional, or general), treatment received (medical or surgical), and hand sequelae. All masses were evaluated according to their shape. If the body had a protruding end, this end was first cut to prevent additional

Cite this paper as:
Akdağ O, Yıldıran G, Karameşe M. Management of huge and extraordinary metal-penetrating injuries to the hand. Turk J Surg 2018; 34: 117-120.

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This study was presented at the "14th National Congress of the Turkish Society for Surgery", Bursa, Turkey.

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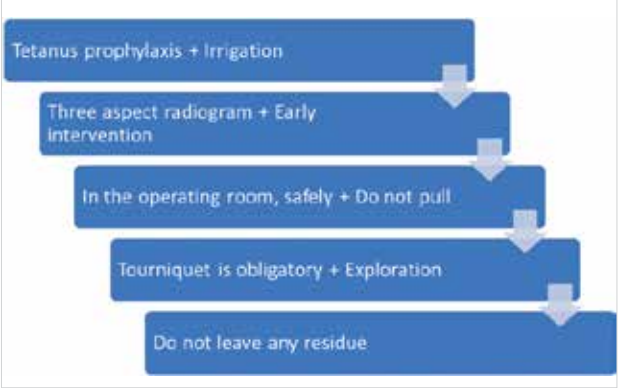
Received: 09.04.2017
Accepted: 26.05.2018

Table 1. Treatment algorithm



injuries while pulling out the body. Thereafter, the end of the metallic mass and the main body were pulled one by one. An approach to manage the foreign metallic bodies penetration was thus clarified (Table 1).

RESULTS

Four females and three males with an age range of 14–51 (mean, 33.5) years were evaluated. Five of seven (71.4%) injuries were home accidents. The causes of injury were knitting hook in three patients, iron fence in two patients, mixer in one patient, and metal nail in one patient. Furthermore, fingers in two, palms in two, wrists in three patients were the affected regions (Figure 1, 2).

Figure 1. a-c. A 23-year-old female patient was admitted with a knitting hook penetrated in her palm (a). There were no neurovascular or skeletal injuries; radiogram (b); the hook was removed not by pulling but by cutting its head (c). No residue was retained

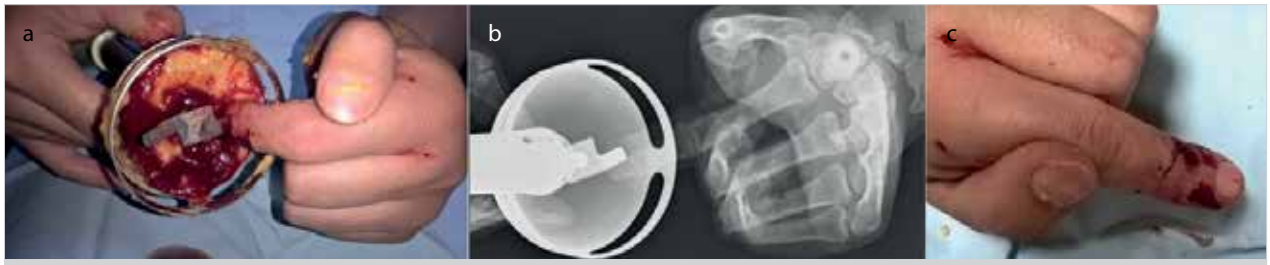


Figure 2. a-c. A 46-year-old female patient was admitted with kitchen mixer penetration in her left hand index finger (a); radiogram (b); the mixer was removed and patient was

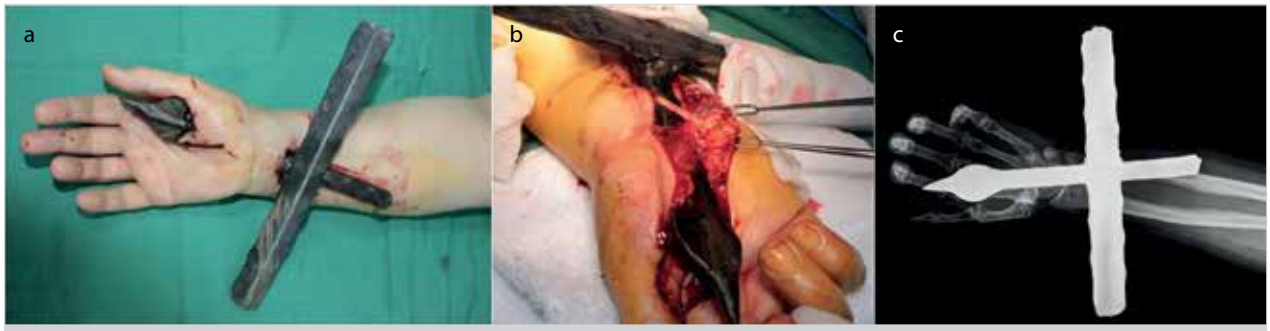


Figure 3. a-c. A 51-year-old female patient was admitted with iron fence penetrated from her wrist to the thenar region of the hand via the carpal tunnel (a); the fence did not cause any neurovascular or tendon injury (b); radiogram (there were no skeletal injuries) (c). Fence was removed completely without any residue

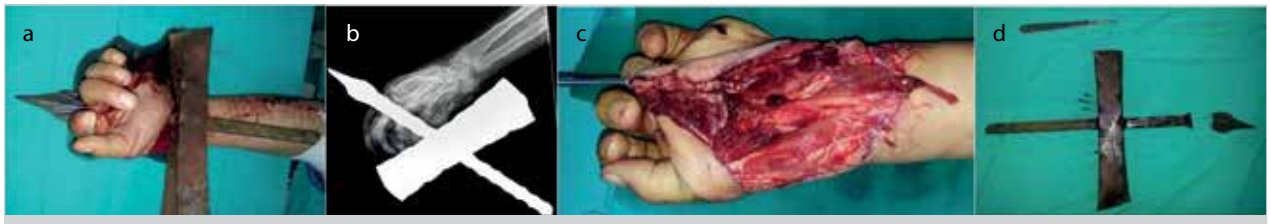


Figure 4. a-d. A 14-year-old male patient was admitted with iron fence penetrated from his thenar region to the second web of the hand (a); radiogram (b); he had flexor pollicis longus, second flexor digitorum longus tendons, and ulnar artery injury. Injured structures were repaired (c); the fence was removed not by pulling but cutting its head without any residue (d). He received rehabilitation for the hand in the early recovery period

Patients' history was obtained, and a detailed hand examination was performed for all patients. In some patients, in whom the penetrating mass was deep and sharp, tendon examination was not performed aggressively (Figure 3, 4).

For all patients, tetanus prophylaxis was administered in the emergency room. Extremities were covered with simple dressing until the patients were shifted to the operating room. Plain radiography was performed for the patients from three aspects, and photographs were captured. All wounds were irrigated. The respective foreign bodies were removed in the operation room on an urgent basis. Three injuries were required to be removed under general anesthesia; four were removed under local anesthesia. For all patients, a pneumatic tourniquet was used. During surgery, all the hand functions were preserved, and patients underwent hand physiotherapy postoperatively. The masses were removed by cutting, and no residue material was left behind. Postoperative radiograms and photographs were captured.

DISCUSSION

Many patients present to emergency services with foreign-body injuries. The most common foreign bodies are wooden splints, metallic fragments, and glass and stone pieces (2). Metallic foreign bodies constitute a majority of the foreign bodies. However, some types of metal foreign bodies that may result much more serious situations are more than only a mass, forming a mechanical load for the hand.

The body's response to foreign mass differs according to the anatomical region, content of the foreign body, time elapsed since penetration of the mass, and if there is tissue hypersensitivity for the foreign body. Foreign bodies that include iron cause less hypersensitivity reactions than those containing aluminum, copper, or mercury (3, 4). Most of our patients injured by iron; however, we examined the injury in the early period and noted no hypersensitivity.

The injury types presented in this study are related to visible foreign bodies. Hence, other clinical scenarios of a differential diagnosis may be negligible. For diagnosis, a minimum of two-way radiograms are crucial (5, 6). However, it should be considered that wood, plastic, glass without silisium, and aluminum are radiolucent (7). In metallic-body injuries, not only skeletal injuries are seen but also the localization and shape of the metallic objects are visualized; thus, radiograms are crucial. For interpreting the exact localization of the foreign body, scopies and markings with needles or wires are useful. Today, imaging systems are advantageous in capturing the images. We obtained three-way radiograms for all our patients to evaluate skeletal injuries, which may occur due to an extraordinary metallic object (Figure 2-4), and to evaluate the exact localization (Figure 1).

We recommend radiograms for masses even if they may be diagnosed by inspection to evaluate for an additional mass, a fractured metallic mass, or a skeletal injury. Besides, radiograms are crucial to evaluate the shape of the penetrated body. If the metallic object has a hook or ends as an arrow, this side should firstly be cut and separated from the main body. If there is a hook or arrow, the metallic object should not be removed by pulling or rotating the main mass because of the high risk of additional injuries. Also, photographs should be taken perioperatively for medicolegal issues in these cases. Because all the masses were visible and metallic, we utilized from 3-aspect-radiograms. However, if residual foreign-body suspicion persists, ultrasonography or computed tomography may be performed (5-8).

After recognizing the metallic body, the patient should be administered tetanus treatment as prophylaxis, and wound irrigation and urgent surgical interventions should be performed (9). We performed urgent surgical intervention in the operating room. Operating rooms are better than emergency rooms in terms of sterility, and both intraoperative and postoperative analgesia can be more easily provided in the operating rooms. We also observed that patients for psychological stability in the operating room. Loco-regional or general anesthesia can be applied. Often, even if regional anesthesia is administered, sedation should be included in the anesthesia for agitated or irritated patients. In the operating room, the metallic object should be removed safely not by pulling or rotating but by cutting. We removed all the foreign bodies by cutting and separating the two ends of the metallic objects from each other. Sometimes, it is necessary to make an extra, small incision for adequate exposure. We made an additional incision in one patient (Figure 3). During this procedure, no residual mass should be left behind. While exploring the hand, all the masses were removed. However, we recommend intraoperative fluoroscopy if there is a doubt of persistent or residual foreign body.

CONCLUSION

It is obligatory to obey the basic rules of removing foreign bodies, such as tetanus prophylaxis and irrigation, in the emergency room. However, for huge and penetrating objects, some additional processes, such as removing the body in the operating room by cutting and without pulling, rotating, or any residual mass, exploration of the hand, and physiotherapy, should be considered while developing the algorithm of removing metallic foreign bodies.

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Informed Consent: Written informed consents were obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.Y., O.A.; Design - G.Y., O.A.; Supervision - O.A., M.K.; Resource - O.A., G.Y., M.K.; Materials - G.Y.; Data Collection and/or Processing - G.Y., O.A.; Analysis and/or Interpretation - G.Y., O.A.; Literature Search - O.A., G.Y.; Writing Manuscript - G.Y., O.A.; Critical Reviews - O.A., M.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 121-124
DOI: 10.5152/turkjsurg.2018.3881

Original Article

Approach to the diagnosis and treatment of mesenteric panniculitis from the surgical point of view

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ABSTRACT

Objective: To evaluate the diagnostic and treatment approaches for patients diagnosed with mesenteric panniculitis

Material and Methods: We retrospectively reviewed all patients diagnosed with mesenteric panniculitis between January 2010 and March 2016. We recorded the demographic features, clinical symptoms, laboratory values, radiological methods, treatment approach, and outcomes of the patients.

Results: We evaluated 22 patients (17 male and five female) with a mean age of 45.8±15.7 years. The most frequent complaint was abdominal pain. The patients' histories included colon cancer (n=1), prostatic cancer (n=2), renal cell cancer (n=1), diabetes mellitus (n=4), and chronic obstructive pulmonary disease (n=1). Laboratory values revealed elevated C-reactive protein levels in 14 patients (43%). Computed tomography was performed in all the patients. Only 10 patients were followed up in the surgical ward, the remaining 12 underwent outpatient treatment. No complication associated with hospitalization or during outpatient follow-up period was observed.

Conclusion: Mesenteric panniculitis can be successfully treated conservatively without surgical intervention. Clinical doubt is of great importance for diagnosis, and plausible underlying malignancy should be kept in mind.

Keywords: Abdominal mass, acute abdomen, conservative approach, mesenteric disorders, mesenteric panniculitis

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Cite this paper as:
Kaya C, Bozkurt E, Yazıcı P, İdiz UO, Tanal M, Mihmanlı M. Approach to the diagnosis and treatment of mesenteric panniculitis from the surgical point of view. Turk J Surg 2018; 34: 121-124.

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Received: 02.04.2017
Accepted: 05.06.2017

INTRODUCTION

Mesenteric panniculitis (MP) is defined as the development of chronic inflammation and necrosis of adipose tissue of the mesentery, resulting in fibrosis. The outcome of MP is usually good (1-3). MP was first described in 1924 by Jura and has also been referred to as sclerosing mesenteritis, liposclerotic mesenteritis, mesenteric lipodystrophy, or mesenteric Weber–Christian disease (4-7). Although a definitive cause of MP has not been defined so far, several comorbidities such as diabetes, hypertension, rheumatic diseases, and particularly abdominal and pelvic malignancies have been reported (8, 9).

Mesenteric panniculitis can be diagnosed with same findings as a large abdominal mass. While the most common symptom is abdominal pain, nausea and vomiting may also be seen. Some patients are diagnosed with only intestinal obstruction. However, most cases incidentally emerge during imaging studies unrelated with the symptoms. Although computed tomography (CT) is not always helpful in the differential diagnosis of MP from primary or secondary mesenteric tumors, some characteristic findings suggest MP (10). The characteristic CT findings of MP are as follows: a tumoral pseudocapsule (a fatty mass separated from the base of the mesentery), an adipose ring (a normal adipose tissue surrounding the mesenteric vessels), and an intra-abdominal mass displaced adjacent bowel loops without invasion (10). As positron-emission tomography is a good alternative method to rule out malignancy for focal mesenteric masses, the most common technique used for diagnosis is CT; however, surgical approach is still the best method for definite diagnosis (11, 12).

In most cases, MP can limit itself and even regression can be seen without medical treatment during follow-up. Clinical symptoms can subside with agents such as corticosteroids, colchicine, cyclophosphamide, and tamoxifen without surgery. MP is considered not to be precancerous, and long-term follow-up is not needed (11). In this study, we aimed to analyze the outcome of patients who were diagnosed with MP and treated.

MATERIAL AND METHODS

We retrospectively reviewed all patients diagnosed with MP between January 2010 and March 2016. Informed consent was obtained from all patients. Patients' demographic characteristics, clinical symptoms, laboratory results, imaging methods, treatment approaches, and outcome were recorded. This study was conducted in accordance with the Declaration of Helsinki.

In our study, in the diagnosis of MP the main radiological findings in CT imaging were as follows: (i) the presence of a nonhomogeneous, well-demarcated fat mass in the mesentery of the small intestine, (ii) including superior mesenteric vessels without invading them, (iii) pushing the intestines to the edge without invasion, and (iv) the presence of lymph nodes with a short axis of <10 mm. The size of the mass, density, calcification status, presence and size of lymph nodes, oil ring sign, and pseudocapsule formation were evaluated.

The results were analyzed using SPSS version 21.0 (Statistical Package for the Social Sciences Inc, IBM, Armonk, NY, USA). The numerical variables were expressed as mean ± standard deviation or median (range) based on the distribution pattern, whereas the categorical variables were presented as absolute values and percentages.

RESULTS

We evaluated 22 patients (17 male and five female) with a mean age of 45.8±15.7 years. Of these patients, nine with severe abdominal pain and high leukocyte levels (41%) were treated by hospitalization, whereas 12 without leukocytosis (59%) were treated as outpatients. The hospitalized patients were treated with 2*1 g daily dosage of cefazolin intravenously (Cefazolin® Bilim Pharmaceuticals, Istanbul, Turkey); the outpatients were followed up with an anti-inflammatory drug treatment, without antibiotherapy.

When the clinical history of the cases was evaluated, three patients had undergone abdominal surgery previously (colon cancer, one patient and prostate cancer, two patients), and one patient was incidentally diagnosed with renal cell cancer. In addition, four patients had diabetes mellitus (DM), and one patient had pulmonary disorder (asthma). When the body mass index (BMI) of the patients was assessed, five had BMI >35 (22.7%) and seven had a BMI of 30–35 (32%). The most common symptom at the time of admission was abdominal pain (90%), whereas the other complaints included fatigue, loss of appetite, nausea, and vomiting. The median C-reactive protein (CRP) level at the time of diagnosis was 26.9 mg/L (range, 0.44–573 mg/L); the mean white blood cell (WBC) count was 10.690±3.504/mL (normal range, 4.500–10.500/mL) (Table 1).

All patients underwent abdominal ultrasonography (USG) and abdominal CT. Only four patients showed findings consistent with MP following USG (18%), whereas all other patients were diagnosed with MP considering CT findings (Figure 1).

Complications related to MP did not occur in any patients during the treatment and follow-up period of 1–6 months. One patient was conservatively treated again after 2 months due to the recurrence of pathology.

Table 1. Characteristics of patients treated for MP

No patients	Age	Sex	Treatment approach.	BMI kg/m^2	Clinical findings	WBC/mL	CRP mg/L	Follow-up (month)
1	40	M	OP-FU	35.5	Abdominal pain, fatigue	19.600	206	6
2	50	M	IH-FU	38.7	Abdominal pain	14.100	26	6
3	48	F	IH-FU	32	Abdominal pain	5.920	0.44	4.5
4	56	F	IH-FU	30.1	Abdominal pain	8.330	121	4
5	48	M	IH-FU	37	Abdominal pain, vomiting	10.200	11	6
6	20	F	OP-FU	24	Abdominal pain, dysuria	8.370	69	2
7	54	M	OP-FU	34.8	abdominal distention, vomiting	13.200	60	6
8	18	M	IH-FU	23.2	Abdominal pain	8.750	3	6
9	52	F	OP-FU	33.1	Abdominal pain	7.949	3.	4
10	70	M	OP-FU	26	Abdominal pain	9.600	149	3.5
11	52	M	OP-FU	29.8	Nausea, vomiting	10.000	27.8	5
12	34	M	OP-FU	28	Abdominal pain	8.330	24	3
13	36	M	OP-FU	41	Malaise	9.840	0.8	6
14	25	F	OP-FU	24.1	Abdominal pain, loss of appetite	10.650	3	5
15	49	M	IH-FU	32	Abdominal pain	16.700	573	6
16	38	M	IH-FU	32.6	Abdominal pain, nausea, vomiting	15.900	58	2.5
17	63	M	IH-FU	23	Abdominal pain	13.500	115	6
18	60	M	OP-FU	40	Abdominal pain	8.500	32	6
19	57	M	OP-FU	33	Abdominal pain	12.000	21	4
20	78	M	IH-FU	29.8	Abdominal pain, loss of appetite, malaise	7.230	4	6
21	33	M	OP-FU	30.5	Abdominal pain	7.980	3.8	1
22	28	M	IH-FU	25.1	Abdominal pain	7.470	32.4	1

BMI: Body Mass Index; CRP: C-reactive protein; WBC: white blood cell; M: Male; F: Female; OP-FU: outpatient follow-up; IH-FU: in-hospital follow-up

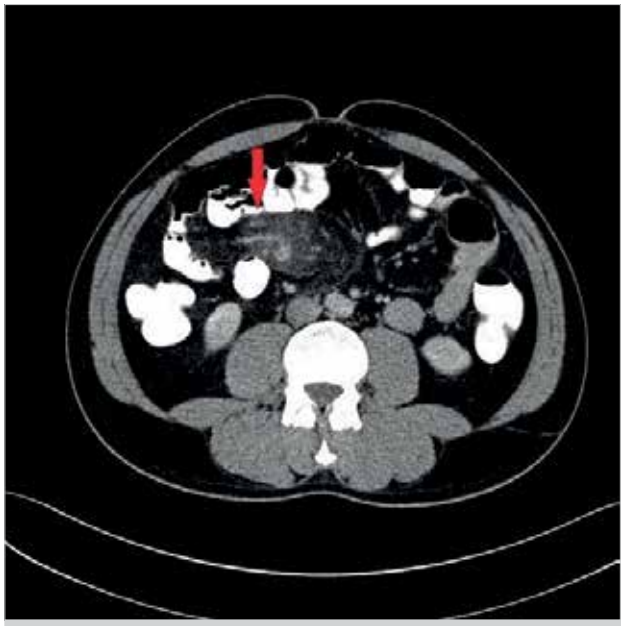

Figure 1. Computed tomography appearance of the increased attenuation in the root of the mesentery and enlarged lymph nodes

DISCUSSION

Mesenteric panniculitis is a nonspecific inflammatory pathological condition affecting the mesenteric adipose tissues of the small and large intestines. In almost all cases, histologically MP has three main components as follows: necrosis of the adipose tissue, chronic inflammation, and fibrosis. These components are reflecting the different phases of the natural course of a single disease (13). Mesenteric disorders are classified based on the main component of the pathology: fat necrosis, fibrosis, and chronic inflammation in the mesentery resulting in mesenteric lipodistrophy, sclerosing mesenteritis, and MP, respectively. The most appropriate diagnostic term for most of the patients with mesenteric disorders is sclerosing mesenteritis due to the varying degrees of fibrosis (14). However, considering our results, the histopathological main component of the patients in our series was mostly chronic inflammation that resulted in acute MP. The etiology of MP is thought to be associated with several diseases. Vasculitis, granulomatous diseases, rheumatic diseases, malignancies, pancreatitis, previous abdominal surgeries or trauma, ischemic injury, and infections are among the underlying conditions (5, 7). The most common causes include autoimmune disorders and malignancy (15, 16). Three patients in our series were diagnosed with a malignancy, whereas four were diagnosed with DM.

Obesity is known to have an association with infection risk and delayed wound healing. The severity and incidence of inflammatory events is higher in obese patients than in those having a BMI of 20–25 kg/m^2, and the antibody response against antigens is weaker (17). The anatomic, metabolic, and biochemical characteristics of adipose tissue can also be the risk factors for intestinal and mesenteric diseases. Our study showed that the overall BMI was high in almost all patients; BMI was between 30 and 35 kg/m^2 in seven patients and over 35 kg/m^2 in five patients. This could be related to obesity-induced immune dysfunction.

In a post-mortem case series with >700 cases of MP, the incidence of MPs was 1%. It was mostly diagnosed in the sixth decade and was found to be two-fold higher in men (18). Although MP is usually located in the small bowel mesentery, the frequency of mesocolon location is approximately 20% (19, 20). The demographic features in our series were consistent with the literature.

The clinical symptoms induced by MP may vary and are nonspecific. The most commonly observed symptoms are abdominal pain and abdominal mass and the less frequently ones are nausea, vomiting, constipation, diarrhea, weight loss, and rectal bleeding (3, 18, 21); however, it can be asymptomatic as well. In our study, all patients were symptomatic; the most common symptom was abdominal pain.

The laboratory values are usually within normal limits. Elevated WBC counts, sedimentation rates, and CRP or anemia have been reported but are not common (22, 23). However, these laboratory values were mostly higher than the normal range in our study. This was why some of the patients were followed up in a surgical ward, although most were treated as outpatients.

Imaging studies have an important role in the diagnosis of MP. Although the abdominal X-ray has no diagnostic value, abdominal USG and CT are of great importance for diagnosis (24, 25). Furthermore, abdominal CT findings may be quite sufficient in the diagnosis of MP due to its high specificity (5). It should be noted that various nonspecific radiological findings of MP such as calcification can also be observed (1, 2, 26). In our study, CT revealed misty mesentery in most of the patients.

There is no consensus on the treatment of MP. Treatment approaches in the literature mostly consist of supportive procedures regarding symptoms. There has been no large randomized controlled study evaluating the efficacy of steroids and immunosuppressive treatment, although clinical improvement was noted with these treatment regimens. Ginsburg et al. (19) reported that three-fourths of symptomatic patients who were administered thalidomide showed a regression of symptoms (22). In our study, patients with comorbidities, significant abdominal pain, and elevated WBC were treated with parenteral antibiotherapy and followed up in the surgical ward. Anti-inflammatory analgesics were administered to the patients who were followed up, and no complications related to MP were seen during the follow-up.

CONCLUSION

Mesenteric panniculitis is one of the rare causes of abdominal pain, and its etiology is still unclear. Diseases affecting the immune system, such as obesity and DM, are thought to be the underlying disorders. Patients diagnosed with MP should be carefully investigated for concomitant diseases, particularly malignancies, with respect to the etiology. Even though there is no consensus about the treatment options, antibiotherapy seems to be an effective treatment option, particularly for patients with elevated inflammatory markers.

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Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.K., E.B., U.O.İ., P.Y.; Design - C.K., E.B., M.T., M.M.; Supervision - C.K., E.B., P.Y., U.O.İ., M.M.; Resource - C.K., E.B., M.T.; Materials - C.K., U.O.İ., M.T., E.B.; Data Collection and/or Processing - C.K., M.T., E.B., U.O.İ., M.M.; Analysis and/or Interpretation - C.K., E.B., P.Y.; Literature Search - C.K., E.B., U.O.İ., P.Y.; Writing Manuscript - C.K., E.B., M.T., P.Y.; Critical Reviews - C.K., P.Y., U.O.İ., M.M.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 125-130
DOI: 10.5152/turkjsurg.2018.3846

Original Article

Survival outcomes after D1 and D2 lymphadenectomy with R0 resection in stage II–III gastric cancer: Longitudinal follow-up in a single center

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ABSTRACT

Objective: D2 lymphadenectomy (D2-LND) with curative resection (R0) is the cornerstone of gastric cancer treatment. In this study, we compared survival outcomes of D2-LDN with D1-LDN in patients who had undergone curative resection for Stages II and III primary gastric adenocarcinoma.

Material and Methods: Between April 1996 and March 2014, 153 consecutive patients with adenocarcinoma of the stomach underwent total gastrectomy with D1-LND or D2-LND. Among those, 118 patients (38 D1 vs. 80 D2) with a complete history and having been followed for at least 1 year after surgery were enrolled.Both groups were compared in terms of demographic and clinico-pathologic characteristics.

Results: The mean follow-up was 42.6±52.5 months (mo.). The demographic characteristics of the groups were similar. The Tumor, Node and Metastases (TNM) stage distribution was 25% for Stage II and 75% for Stage III for both groups. Eighteen patients (47.4%) in the D1 and 47 patients (58.8%) in the D2 group were free from locoregional recurrence. The median disease-free survival was 22.0±4.1 mo. for the D1 and 28.0±4.3 mo. for the D2 group (p=0.36). Eight patients (21%) in the D1 and 39 patients (49%) in the D2 group were alive at the last follow-up. The median overall survival (OS) was 22.0±3.7 mo. for the D1 and 31.0±5.4 mo. for the D2 group (p=0.13). The 5-yeardisease-free survival and OS by the Kaplan–Meier estimates were 41% vs. 51% and 30% vs.42% in the D1 and D2 groups, respectively. The median 5-year OS for patients with Stages IIIB and IIIC tumors was 14.0±2.2 mo.for the D1 and 20.0±5.0 mo. for the D2 group, respectively (p: 0.048).

Conclusion: When compared to D1-LND, D2-LND with R0 resection have yielded a trend toward a better outcome in patients with primary gastric adenocarcinoma.

Keywords: R0 resection, D1 lymph node dissection, D2 lymph node dissection, total gastrectomy

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Cite this paper as:
Uslu A, Zengel B, İlhan E, Aykas A, Şimşek C, Üreyen O, Duran A, Okut G. Survival outcomes after D1 and D2 limphadenectomy with R0 resection in stage II–III gastric cancer: longitudinal follow-up in a single center. Turk J Surg 2018; 34: 125-130.

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Received: 19.02.2017
Accepted: 12.06.2017

INTRODUCTION

In the current era, both in Eastern and in Western populations, curative resection (R0) with D2 lymphadenectomy is accepted as the standard treatment for stomach cancer (1). The incorporation of D2 lymph node dissection (D2-LND) in routine practice has been materialized since 1960 in Japan and Korea, while it has recently appeared in Western guidelines (2, 3). Western surgeons were so far reluctant to establish D2 as a routine practice because of the reported-at least 10%-surgical mortality in two prospective randomized trials, while it was less than 3% in Japan for more than three decades (4, 5). However, this excess mortality was basically due to additional extended surgery, essentially the splenectomy with or without pancreatectomy. Besides, the best survival was obtained in patients who underwent spleen-sparing D2 resections (6, 7). A recent meta-analysis of eight prospective randomized trials including more than 2000 patients revealed a trend toward lower gastric-cancer-related mortality in patients who underwent D2 resection without splenopancreatectomy (8).

In this study, we evaluated the efficacy of limited (D1-LND) versus extended lymphadenectomy (D2-LND) for a consecutive group of patients with gastric adenocarcinoma, having been treated in a subspecialized oncologic surgery unit during the last two decades.

MATERIAL AND METHODS

Among 256 consecutive patients with adenocarcinoma of the stomach having been treated in University of Health Sciences, Izmir Bozyaka Research and Training Hospital, Department of General Surgery between April 1996 and March 2014, 103 patients were excluded because of the implemented palliative measures including subtotal gastrectomies, insertion of enteral feeding catheters and all bypass procedures, resections lesser than D1, and pathological assessment indicating Stage I tumors or R1 resections.

The inclusion criteria of the study were primary gastric adenocarcinomas with radiologic evidence of locoregional disease, total gastrectomy with D1 or D2 lymphadenectomy with ultimate pathology re-

Table 1. Adjuvant chemotherapy regimens and radiotherapy

Adjuvant Chemotherapy	D1-LND* group (n=38)	D2-LND** group (n=80)	p
Not received	2 (%5.3)	16 (%20.0)	0.053
MAYO protocol	9 (%23.7)	29 (%36.2)	
CISPLATIN+UFT protocol	17 (%44.7)	18 (%22.5)	
DCF*** regimen	10 (%26.3)	17 (%21.3)	
Adjuvant radiotherapy (+)	26 (68.4%)	52 (65%)	0.71

*D1-LND: D1 lymphadenectomy
**D2-LND: D2 lymphadenectomy
***DCF: docetaxel, cisplatin, 5 fluorouracil
pts: patients

Table 2. The demographic and clinico-pathological characteristics

Age (years)	58.6±11.9	62.5±12.3	0.11
Gender:			
Male	28 (73.7%)	54 (67.5%)	0.495
Female	10 (26.3%)	26 (32.5)	
Co-morbid disease	15 (39.5%)	30 (37.5%)	0.84
Additional organ surgery	2(5.3%)	4(5%)	0.63
TNM Stage			
IIA and IIB	9(23.7%)	20(25%)	0.62
IIIA	10(26.3%)	15(18.8%)	
IIIB	6(15.8%)	20(25%)	
IIIC	13(34.2%)	25(31.3%)	
Signet-ring cell, mucinous and poorly differentiated histology	15(39.5%)	30(37.5%)	0.84
Lymphovascular and neural invasion	20 (52.6%)	42 (52,5%)	0.99
Location of tumor:			
1/3 proximal stomach	7(18.4%)	21(26,3%)	0.009
1/3 mid-stomach	24(63.2%)	27(33,8%)	
1/3 distal stomach	7(18.4)	32(40%)	
Number of retrieved lymph nodes	27.5±14.3	35.7±18.8	0.02

*D1-LND: D1 lymphadenectomy
**D2-LND: D2 lymphadenectomy

Table 3. The distribution of morbidity and mortality in the D1 lymphadenectomy and D2 lymphadenectomy groups

	D1-LND* group (n=38)	D2-LND** group (n=80)
Bacterial pneumonia	9 (23.6%)	5 (6.3%)
Minor leak from the esophagojejunal anastomosis	2 (5.3%)	5 (6.3%)
Duodenal stump leakage	2 (5.3%)	2 (2.4%)
Death	-	1 (1.2%)

*D1-LND: D1 lymphadenectomy
**D2-LND: D2 lymphadenectomy

porting R0 resection,at least 15 nodes removed in the D2 cohort Stages II and III tumors based on the 7th edition of the UICC/AJCC criteria (9), and no neoadjuvant chemotherapy ± radiotherapy.

Thus, 153 patients were eligible for the final analysis. Of those, 118 patients (38 D1 vs. 80 D2) who have survived at least 1 year after surgery were enrolled in the study. Thirty-five patients were excluded because they were lost to follow-up, incomplete clinical history, incompliance during adjuvant therapy, or short-term follow-up. Surgical quality was assessed solely by the pathological confirmation of R0 resection in standard D1 and D2 lymphadenectomy. This prevented the contamination of results by disparities of surgical skills and techniques. Clinical database and follow-up information were complete for the whole study group. In-hospital mortality is defined as the number of deaths from any cause within 30 days of surgical intervention.

Written informed consent was obtained from patients who participated in this study. The research was conducted according to the principles of the World Medical Association, the Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," (amended in October 2013).

Surgical Procedures and Quality Assessment

The methodology of D1 and D2 resection was essentially based on the guidelines of the Japanese Research Society for the Study of Gastric Cancer (10). The details were explained in a previous study by our group, elsewhere. The sine qua non of quality was the ultimate pathology report indicating R0 resection with the removal of at least 15 lymph nodes in D2 gastrectomy (11). All patients underwent total gastrectomy through the Roux-en-Y reconstruction. Esophagojejunostomyanostomosis was performed by a circular stapler or by hand in the D1 group, but unexceptionally by hand-sewn single-layer 3:0 atraumatic single sutures in the D2 group.

Adjuvant Chemotherapy and Radiotherapy

Adjuvant chemotherapy was conducted when possible in all patients having the SWOG performance status score between 0 and 2. While almost all patients with Stage IIA (T3N0M0, T2N1M0) have received the Mayo regimen, patients with pathological T1N2M0 and Stage IIB or greater receiveda cisplatin-based regimen ora docetaxel-containing regimen after 2011, when possible.

The chemotherapy protocols with the distribution of chemotherapy and radiotherapy among the D1 and D2 groups are shown in Table 1. The Mayo regimen consisted of 5FU plus a low-dose leucovorin (5FU 425mg/m^2 plus leucovorin 20mg/m^2) intravenous push daily for 5 days with courses repeated at 4-week intervals. Cisplatin (CDDP) plus an UFT regimen consisted of intravenous CDDP 30 mg/m^2 administered on Days 1–3 and a single oral UFT dose of 400 mg/m^2/day administered on Days 1 through 28, and they were repeated every 28 days. Docetaxel has been administered to patients since 2011, which is when itwas approved for use in adjuvant treatment of gastric cancer. DCF consisted of docetaxel (75mg/m^2 day 1), CDDP (75mg/m^2 day 1), and 5FU (750mg/m^2 by 24-h continuous infusion for 5 days) administered every 3 weeks in 6 cycles.

All patients who had pT3, T4, and pN+ were referred for radiotherapy. However, 2 patients in the D1 and 8 patients in the D2 group did not receive or complete radiotherapy due to a low clinical performance, advance age, or treatment adverse effects.

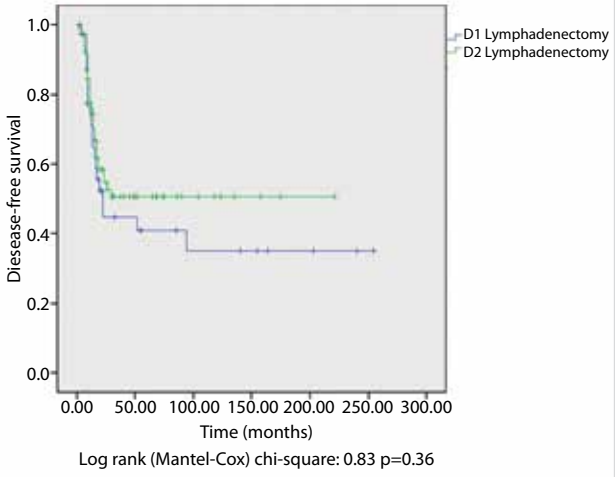

Figure 1. The Kaplan–Meier disease-free survival curve

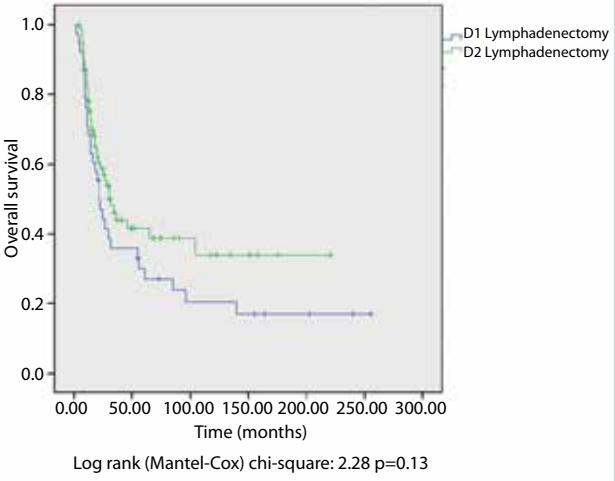

Figure 2. The Kaplan–Meier overall survival curve

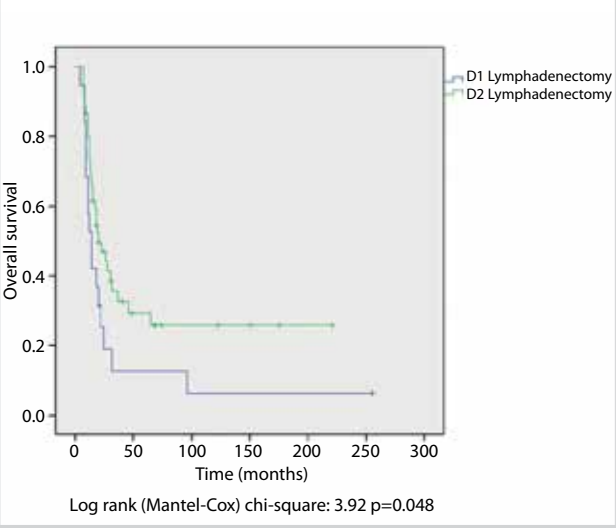

Figure 3. The Kaplan–Meier estimate of the overall survival for the pathologic stages IIIB and C patients in the D1 lymphadenectomy vs. D2 lymphadenectomy groups

Statistical Analysis

Overall survival (OS) and disease-free survival (DFS) were defined as the time from D1 or D2 resection to death and to the occurrence of the first locoregional recurrence or distant organ metastasis, respectively.

We calculated the OS and DFS status using the Kaplan–Meier method. Log-rank tests were performed to compare OS and DFS. Independent two-sample t-test was used to detect the differences among demographic data and histopathological variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The demographic and clinico-pathological characteristics of the patients are shown in Table 2. There was no difference between demography of the groups with respect to age, gender, the UICC TNM stage, co-morbid disease and additional organ surgery, the rate of poorly differentiated tumor histology and protocol, and total sessions of adjuvant chemotherapy and radiotherapy. The anatomic location of the primary tumor was predominantly the middle one-third of the stomach in the D1 group (63%) and distal one-third in the D2 group (40%) (p=0.009). As expected, the number of retrieved lymph nodes was significantly higher in the D2 group (p=0.02).The TNM stage distribution was 25% Stage II and 75% Stage III for both groups. Extended surgery was applied in two patients from the group D1. One had distal one-third esophagectomy, and the other had splenectomy with segmental colon resection. Four patients from the D2 group underwent splenectomy, distal pancreatectomy, segmental resection of the transverse colon, and the liver segment III resection, respectively. In-hospital mortality was 0.8% (1 patient).

Postoperative Complications

The most frequent morbid event was post-operative bacterial pneumonia, which occurred in 9 (23.6%) and 5 (6.3%) cases in the D1- and D2-LND groups, respectively. All patients had uneventful course by proper antibiotics, pulmonary toilet, oxygen supplementation, and respiratory exercises.

A minor anastomotic leak at esophagojejunal anostomosis occurred in 2 (5.3%) and 5 (6.3%) patients in the D1 and D2-LND groups. Two patients in the D2-LND group required jejunal stent replacement and 3 weeks of enteral nutrition. Of those, one had subphrenic abscess and was treated successfully by percutaneous catheter drainage. The remaining patients completely recovered by cessation of per-oral feeding, accompanied by 2 weeks of parenteral nutrition. Duodenal stump leakage was observed in 2 cases for both groups. All stumps were closed by linear-staplers. These 2 patients recovered uneventfully with conservative measures.

One patient died suddenly at home 32 days after the operation. He had congestive cardiomyopathy with ejection fraction of 35%. Although we think the death was of cardiac origin, the exact cause of death determined by an autopsy is not available. The distribution of morbidity and mortality in the D1 and D2 groups are shown in Table 3.

Survival Analysis

The mean follow-up was 42.6±52.5 months (mo.). Eighteen patients (47.4%) in the D1 and 47 patients (58.8%) in the D2 group were free from locoregional recurrence or distant organ metastasis. The median DFS was 22.0±4.1 mo. for the D1 and 28.0±4.3 mo. for the D2 group (p=0.36) (Figure 1). Eight patients (21%) in the D1 and 39 patients (49%) in the D2 group were alive at the last follow-up. The median OS was 22.0±3.7 mo. for the D1 and 31.0±5.4 mo. for the D2 group (p=0.13) (Figure 2).

Although a statistical survival advantage has not been obtained for all patients with the D2 lymph node dissection, an overall survival difference in favor of a D2 dissection has emerged for the pathologic stages IIIB and IIIC patients in the subgroup analysis. Nineteen patients in the group D1 and forty-five patients in the group D2 had pathologically assessed stage IIIB and IIIC tumors. The median 5-year OS was 14.0±2.2 mo.for the D1 and 20.0±5.0 mo. for D2 groups with a corresponding p-value of 0.048 (Figure 3).

DISCUSSION

In this study, compared to D1-LND, D2-LND with R0 resection have yielded to a trend toward better survival outcomes in patients with primary gastric adenocarcinoma. The five-year DFS and OS by the Kaplan–Meier estimates were 41% vs. 51% and 30% vs. 42% in the D1 and D2 groups, respectively. There was an absolute 10% difference in favor of the D2 group with respect to the 5-year DFS and OS, but this has not reached statistical significance. These results are derived from a prospectively collected database of a single oncological surgery unit in which surgery, adjuvant chemotherapy, and routine follow-up have been carried through with a multidisciplinary approach for years. The number of the lymph nodes retrieved in this study meets the precondition of the new classification system that underlines the strong association between the survival outcomeand the lymph node count (12) and reveals the quality of surgery.

As demonstrated in the latest randomized controlled trials, the rationale underlying D2 dissection is the ability of the procedure to cure almost 20% of patients with N2-disease (13). In addition, post-hoc analysis of randomized trials in a recent meta-analysis of extended lymphadenectomy for gastric cancer suggested a possible survival benefit in Stage T3+ tumors, non-randomized comparisons revealed the benefit in Stage II and IIIA, and observational studies reported better survival outcomes of D2 surgery (14). In a recent retrospective study conducted on 533 gastric cancer patients, the median survival by Stages IIIB and IIIC were 28.0 and 14.8 mo., and D2-LND appeared as the major prognosticator of survival (15). These findings are consistent with our results in which patients with gastric cancer and the pathological Stage III and beyond, that had at least a loco-regional or a distant metastases, had benefited much from D2-LND with regard to OS, with a median OS of 20.0±5.0 months.

In contrast to equivalent survival outcomes of common solid tumors such as colorectal and breast cancer in the Eastern and Western societies, the West has worse out comes of gastric cancer surgery compared with Japanese trials (5, 13, 14, 16). The mortality rate of D2 dissection is still improving, and it is almost 0.8% in Japan, with a cumulative 5-year survival of 70%, thus bringing D2 dissection as standard routine surgery for cT1N+ and potentially curable cT2-T4 disease (17-19). Two meta-analyses of randomized controlled trials comprised of nearly 1900 and over 2000 gastric cancer patients favored D1 over D2, essentially in terms of significantly reduced postoperative complications and a 30-day mortality rate, with no significant difference in the 5-year survival between the groups (20, 21). These reports and the observation of 10%~13% perioperative mortality with a 5-year survival of 33%~35%, which did not meet the expectations in two major European trials (22, 23), have lead Western proponents to recommend at least D1 dissection, but not to favor a routine application of D2 universally at present (24, 25).

The difference in the survival outcome has been partially attributed to an earlier diagnosis and less aggressive biology of tumors in the East, but this thesis was subsequently refuted via reports indicating a better outcome in patients with comparable pathological stages in the East than in the West. Two studies from the Memorial Sloan-Kettering Cancer Center demonstrated survival differences for T1–T3 tumors in favor of Japanese patients and improved survival after matching by T stage and location in Korean patients compared to the US patients (26, 27). However, as observed in our recent and previous study, it is promising that the inconsistency of the surgical approach between Japan and the Western groups, particularly in terms of the extent of nodal resection, is being eliminated, such that better outcomes in the D2 groups with an operative mortality rate of less than 4% and an increased rate of cases having at least 15 lymph nodes removed is being reported both in randomized control trials and observational studies by surgical teams who had acquired experience through the years spent in Western countries (11, 28-36). The results of the Dutch and UK trials have been criticized for the unacceptably high mortality and poor survival rates, as well as the non-compliance of surgeons (24). On the contrary, Italian Gastric Cancer Study Group reported 2.2% operative mortality in D2-LND and have proven that they can doas well as the Eastern surgeons. Moreover, they have demonstrated the survival advantage resulting from D2 surgery, particularly for patients with the pT2-4 status and positive lymph nodes (32).

CONCLUSION

Therefore, in view of our results and current literature mentioned above, we may conclude the following:

The operative mortality after D2 gastrectomy can be reduced via surgical subspecialization, and D2-LND is already being performed safely by many Western surgical teams. Although a clear-cut evidence about the cumulative survival advantage of D2-LND is still lacking, patients who are perceived to be in an advanced stage, but without distant metastasis, seem to benefit from D2 surgery.

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.

Author Contributions: Concept - A.U., B. Z.,; Design - A.U.; Supervision - B. Z., E.I., A.A.; Resource A.U., B.Z., E.I., A.A.; Materials - A.U., B.Z., E.I.; Data Collection and/or Processing - B.Z., E.İ., A.A., O.U.; Analysis and/orInterpretation - A.A., O.U., C.S., A.D., G.O.; Literature Search - B.Z., E.I., C.S., O.U.; Writing Manuscript - A.U., B.Z., A.D., G.O.; Critical Reviews - E.I., A.A.

Acknowledgements: We would like to thank Raika Durusoy, from Department of Public Health, Ege University School of Medicine for statistical analysis.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 131-136
DOI: 10.5152/turkjsurg.2018.3856

Original Article

Where do these guests come from? A diagnostic approach for metastatic lymph nodes

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ABSTRACT

Objective: In cases presenting with lymphadenopathies (LAP) without a primary focus detected by simple radiological methods, the primary tumor can be diagnosed by a histopathological evaluation of the metastatic lymph nodes. We aimed to discuss the nonhematological malignancies presenting with lymphadenopathies and the histopathological results for primary tumors.

Material and Methods: In this retrospective study, cases diagnosed with metastasis in excisional lymph nodes between January 2013 and June 2016 were assessed for a histopathological diagnostic approach

Results: Among 632 lymph node biopsies, a total of 21 cases, involving 12 male and 9 female patients with a mean age of 57.23 y (range, 33–92 y), of nonhematological solid tumors were included. The most common localizations of the involved lymph nodes were inguinal (n=8), axillary (n=6), cervical (n=4), and supraclavicular (n=3) region. The most common primary tumors were malignant melanoma (n=6), breast carcinoma (n=4), ovarian carcinoma (n=2), squamous cell carcinoma (n=2), and germ cell tumor (n=2). Others were papillary thyroid carcinoma, renal cell carcinoma, urothelial carcinoma, prostate adenocarcinoma, and endometrial adenocarcinoma.

Conclusion: Nonhematological malignancies presenting with lymphadenopathies are one of the most complicated cases for clinicians. The histopathological evaluation of the excisional metastatic lymph node biopsies is an important method because of cost effectiveness and easy applicability.

Keyword: Immunohistochemistry, lymph node metastasis, unknown primary tumor

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Cite this paper as:
Dere Y, Ekmekçi S, Çelik S, Çelik Öİ, Dere Ö, Karakuş V. Where do these guests come from? A diagnostic approach for metastatic lymph nodes. Turk J Surg 2018; 34: 131-136.

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Received: 28.02.2017
Accepted: 12.06.2017

INTRODUCTION

Lymph node metastasis is the most common mode for the spread of carcinomas and solid tumors, such as malignant melanoma (1). Although many radiological and scintigraphy methods were being used for the diagnosis of solid tumors, an excisional biopsy of metastatic lymph nodes can still be necessary especially for oncological treatment procedures (2). In addition, some of the primary tumors presented with lymphadenopathies (LAP) could not be located by imaging. Moreover, the primary foci of malignant melanoma and germ cell tumors can be burnout tumors, which can only be diagnosed by an excisional biopsy of the involved lymph nodes.

Metastatic lymph nodes usually present as palpable masses but can be found by physical examination or imaging studies of patients by investigating for various symptoms (2). In asymptomatic cases, palpable LAP is generally very striking for both clinicians and patients and allows systemic evaluations. However, an excisional biopsy of these enlarged lymph nodes can also be a diagnostic approach for uncertain imaging results.

In this study, we aimed to assess the nonhematological malignancies presenting with LAP and reveal the histopathological approach for the diagnosis of the primary focus.

MATERIAL AND METHODS

All lymph node excisional biopsies (n=632) performed between January 2013 and June 2016 were assessed retrospectively. Every case was investigated for the diagnosis of a known primary focus from hospital records and medical history. Patients with known solid primaries and lymph node metastases diagnosed synchronously with the primary tumor (n=144) were excluded. Cases presenting with lymph node enlargement and diagnosed as any form of hematological malignancies (n=109) or any form of reactive hyperplasia (n=310) and specific infections (n=48) were also excluded. The demographic features and localizations of the lymph nodes were obtained from pathology reports.

Cases with palpable masses were examined by the applied clinicians, and first-step radiologic tests, such as X-ray, ultrasonography (USG), and mammography, were performed; in cases where no explanatory result was found for lymph node enlargement, an excisional biopsy was offered to the patients.

The indications of lymph node excision determined by the clinicians were as follows:

- Primary tumor not assessed using physical examination and first-step imaging studies (X-ray, USG, or mammography)
- Negative biopsies from possible primaries
- Suspicious cases for hematological or nonhematological malignancies

None of the patients underwent positron emission tomography/computerized tomography (PET/CT) before the excision of the enlarged lymph nodes.

Cases diagnosed as reactive LAP or hematological malignancies in addition to patients treated at another center or unavailable for follow up were excluded. Written informed consent was obtained from patients before the operation who participated in this study.

The hematoxylin–eosin stained slides of excisional biopsies were examined in addition to the slides analyzed by immunohistochemistry (IHC). All cases were immunohistochemically analyzed using the (Leica Bond Max®, Leica Biosystems, Germany) automated staining procedure. Antibodies used for IHC analysis was chosen systematically according to the morphological appearance of the entities encountered in the pathological differential diagnosis. The final diagnosis was provided according to histopathological and IHC results followed by a confirmation of the primaries using radiological methods.

RESULTS

A total of 21 cases diagnosed with nonhematological solid tumor presented as lymph node enlargement between January 2013 and June 2016 were assessed retrospectively. The mean age was 57.23 y (range, 33–92 y), and 12 patients were males and 9 were females.

Clinical Approach

The localizations of the enlarged lymph nodes were inguinal (8 cases), axillary (6 cases), cervical (4 cases), and supraclavicular (3 cases). All patients applied with palpable mass, except 2 cases that were presented with inguinal pain and were diagnosed as prostatic adenocarcinoma and renal cell carcinoma.

All of the female patients (n=9) were assessed by breast and axillary examination followed by mammography and breast USG as the first step in the diagnostic approach. Male patients with axillary lymph node enlargement (n=2) were also examined using breast USG. Additionally, 3 cases were reported as those of metastatic epithelial tumor using fine needle aspiration cytology followed by the excision of the involved lymph node, and the final tumor type was evaluated by a histopathological assessment. None of the cases were diagnosed before the excision of the lymph node. No sarcomatous tumor was found among all the metastatic lymph nodes.

Histopathological Evaluation and IHC Analysis

The most common metastatic tumor presented with LAP was malignant melanoma (n=6; Figure 1a and 1b), followed by breast carcinoma (n=4; Figure 1c and 1d), squamous cell

Table 1. Characteristics of metastatic lymph nodes

Age (y)	Sex	Localization	Symptom	Diagnosed primary
79	Male	Supraclavicular	Palpable mass	Squamous cell carcinoma
64	Male	Supraclavicular	Palpable mass	Squamous cell carcinoma
33	Male	Axillary	Palpable mass	Malignant melanoma
63	Male	Cervical	Palpable mass	Malignant melanoma
62	Male	Supraclavicular	Palpable mass	Malignant melanoma
76	Male	Axillary	Palpable mass	Malignant melanoma
42	Male	Inguinal	Palpable mass	Germ cell tumor
50	Male	Inguinal	Palpable mass	Malignant melanoma
38	Male	Inguinal	Inguinal pain	Renal cell carcinoma
78	Male	Inguinal	Inguinal pain	Prostate adenocarcinoma
86	Male	Inguinal	Palpable mass	Urothelial carcinoma
45	Male	Inguinal	Palpable mass	Germ cell tumor
34	Female	Axillary	Palpable mass	Breast carcinoma
92	Female	Axillary	Palpable mass	Breast carcinoma
41	Female	Cervical	Palpable mass	Breast carcinoma
62	Female	Inguinal	Palpable mass	Endometrial adenocarcinoma
40	Female	Cervical	Palpable mass	Malignant melanoma
63	Female	Inguinal	Palpable mass	Ovarian serous carcinoma
56	Female	Axillary	Palpable mass	Ovarian serous carcinoma
36	Female	Axillary	Palpable mass	Breast carcinoma
62	Female	Cervical	Palpable mass	Papillary thyroid carcinoma

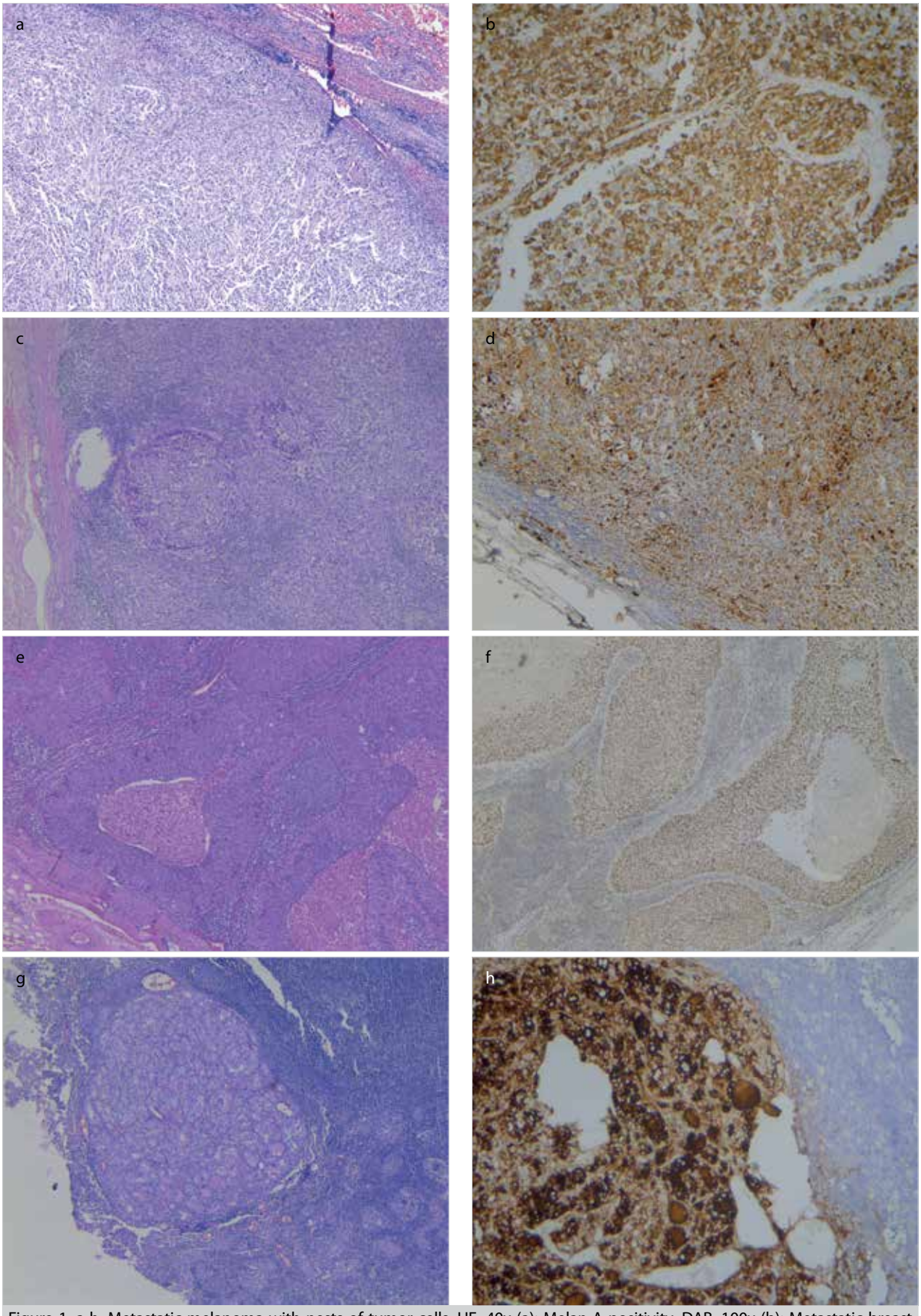

Figure 1. a-h. Metastatic melanoma with nests of tumor cells, HE, 40x (a); Melan-A positivity, DAB, 100x (b); Metastatic breast carcinoma, sheets of tumor cells , HE, 40x (c); GCDFP-15 positivity, DAB, 40x (d); Metastatic high grade urothelial carcinoma, HE, 40x (e); GATA-3 positivity, DAB, 40x (f); Metastatic papillary thyroid carcinoma, HE, 40x (g); Thyroglobulin positivity, DAB, 100x (h)

Table 2. Histopathological and immunohistochemical features of the metastatic tumors

Primary tumor	Histological features	IHC features	Additional parameters
Melanoma	Tumoral nests of cells with conspicuous nucleoli and numerous mitotic figures	HMB-45(+), S100 (+)	Melanin pigment (+)
Breast carcinoma	Tubules and solid tumoral areas	GCDFP-15 (+), CK 7(+), ER/PR (+)	-
Squamous cell carcinoma	Tumoral squamous cell nests with keratinization and keratin pearls	p63(+), HMWCK(+), CK20(–), TTF-1(–)	-
Prostatic adenocarcinoma	Cribriform malignant glandular structures	PSA (+),AMACR(+), CDX2(–)	Gleason score 4+4 (Grade group 4)
Papillary thyroid carcinoma	Tumoral cells showing papillary configuration with ground glass nuclei, nuclear grooves, and overlap	TTF-1(+), CK7(+), Thyroglobuline (+)	-
Ovarian carcinoma	Tubular, adenoid, and papillary configuration of pleomorphic tumoral cells showing conspicuous nucleoli	CK7 (+), WT1 (+), CA125 (+), CK20 (–), TTF-1 (–), CDX2 (-), GCDFP-15 (–)	-
Renal cell carcinoma	Tumoral cell nests with clear cytoplasm and conspicuous nucleoli	EMA (+), CD10 (+), Vimentin (+), PAX8 (+), CK7 (–), PSA (–), CDX2 (–)	-
Germ cell tumors	Cords and sheets of uniform but malignant cells surrounded with lymphocytic infiltration	OCT 3/4 (+), CD117 (+), PLAP (+)	-
Endometrioid adenocarcinoma	Epitheloid tumor characterized by solid sheets of round cells showing prominent nucleoli	pan CK (+), Vimentin (–), ER (+)	-
Urothelial carcinoma	Tumoral cords and columns with cells showing conspicuous nucleoli and hyperchromatic nuclei	CK 20 (+), GATA3 (+), Uroplakin III (+), CK7 (–), HMB45 (–), PSA (-), TTF-1 (–), OCT 3/4 (–), CDX2 (–)	-

HMB45: Human melanoma black-45; GCFDP-15:Gross cystic disease fluid protein-15; CK7: cytokeratin 7; ER: estrogen receptor; PR: progesterone receptor; HMWCK: high molecular weight cytokeratin; CK20: Cytokeratin 20; TTF-1: thyroid transcription factor-1; PSA: prostate specific antigen; AMACR: Alpha-methyl CoA Racemase; CDX2: Cluster of differentiation X2; WT1: Wilms tumor 1; CA 125: cancer antigen 125; EMA: epithelial membrane antigen; CD 10: Cluster of differentiation 10; PAX 8: Paired box gene 8; OCT 3/4: octamer-binding transcription factor 3/4; CD117: Cluster of differentiation 117; PLAP : placental alcaline phosphatase; Pan CK: pancytokeratin; GATA 3: GATA Binding Protein 3

carcinoma (SCC; n=2), and ovarian carcinoma (n=2). Other metastatic tumors were urothelial carcinoma (Figure 1e and 1f), papillary thyroid carcinoma (Figure 1g and 1h), renal cell carcinoma, prostatic adenocarcinoma, endometrial adenocarcinoma, and germ cell tumor (n=2).

Malignant melanoma as the most common metastatic tumor metastasized to axillary (n=2), cervical (n=2), inguinal (n=1), and supraclavicular (n=1) lymph nodes. Other tumors and involved lymph nodes are given in Table 1. Histopathological characteristics and IHC features are summarized in Table 2. Frequencies and descriptive statistics were done by SPSS software v20, IBM, USA.

Clinical Evaluation and Radiological Findings After Histopathological Diagnosis

None of the cases diagnosed with metastatic melanoma underwent detailed dermatological examination. After the diagnosis, only one case had a scalp lesion and the excision of the lesion showed melanoma with a Clark level of IV and a Breslow thickness of 2.4 cm. Other metastatic melanoma cases had no primary foci and were accepted as burnout primaries.

None of the female patients with axillary lymph nodes had any breast lesion detected by USG and mammography before the excision. After the diagnosis, all metastatic breast carcinoma cases had breast magnetic resonance imaging (MRI) and mammarian masses were detected with sizes in the range of 1.2–1.8 cm.

The cases with SCC had high-resolution lung CT and/or PET/CT for detecting the primary foci. One of the cases had shown lung primary and the other case had a 5 cm mass located in the renal pelvis biopsied using ureterorenoscopy and diagnosed as high-grade urothelial carcinoma with extensive squamous differentiation.

Metastatic ovarian carcinomas showed bilateral lobulated, contrasted cystic masses with sizes of 23×34 mm and 46×61 mm in the ovarian region on PET/CT. After the operation, the final diagnosis was ovarian serous carcinoma. Another case presented with axillary lymph node involvement had negative results in mammography and breast MRI, and the excision of the lymph node was performed with a suspicion of hematological malignancy. However, after the diagnosis of metastasis, the PET/CT showed a heterogenous cystic lesion of 5.5 cm size in the left ovarian region and extensive intra-abdominal metastatic lymph nodes, and the diagnosis was confirmed after the operation as ovarian high-grade serous carcinoma.

A 50-year-old female patient with axillary metastasis was investigated using mammography and breast USG; however, no mass was detected. After the excision of the lymph node with a suspicion of metastasis of occult breast carcinoma, the final diagnosis was of metastatic ovarian serous carcinoma. The diagnosis was confirmed by lower abdominal CT showing left ovarian cystic mass, which was operated and diagnosed as ovarian serous carcinoma with a size of 44×32 mm and having a thin septae.

The case of metastatic urothelial carcinoma was then confirmed by cystoscopic samples of highgrade urothelial carcinoma with muscularis propria and extensive urothelial carcinoma in situ.

The case of papillary thyroid carcinoma was examined using USG and diagnosed as multinodular goiter with a maximum size of the nodule as 1.2 cm. The fine needle aspiration biopsy (FNAB) performed upon both the thyroid and the lymph node was benign, and the lymph node was subsequently excised. After the diagnosis of the metastatic lymph node, total thyroidectomy was performed and papillary carcinoma was diagnosed at three different foci with a maximum size of 1.2 cm showing capsular invasion. The case applied with inguinal pain was operated for inguinal hernia, and an enlarged lymph node was detected during the operation. After the diagnosis of metastatic prostatic adenocarcinoma, rectal examination revealed enlarged, hard prostatic tissue with a slight increase of prostatespecific antigen (PSA; 4.7 ng/mL).

A 38-year-old male applied with inguinal pain, and the enlarged inguinal lymph node was excised because of the suspicion of a hematological malignancy. After the diagnosis of metastatic renal cell carcinoma, detailed imaging studies revealed a cortical, 3.8 cm-sized, solid renal mass located in the upper lobe of the right kidney. After radical nephrectomy, a clear cell renal cell carcinoma of Fuhrmann grade 3 with vascular invasion was detected.

In one of the 2 cases of metastatic germ cell tumor, a 2.4 cm-sized mixed germ cell testicular tumor (seminoma, 70%; embryonal carcinoma, 30%) with necrosis was detected through orchiectomy. The other case showed a fibrohyalinized nodule located in the right testis with no alive tumor cells. The morphological features were concordant with burnout tumor.

DISCUSSION

Nonhematological malignancies presenting with lymph node enlargement are one of the most confusing cases for clinicians. A standard diagnostic approach for enlarged lymph nodes should consider detailed medical history, physical examination, clinical symptoms and findings, laboratory and imaging studies, and histopathological evaluation using IHC analysis (2).

Radiological studies have diagnostic limitations of about 30%–50% for various tumor types (3). However, MRI has a chance of tumor detection of about 70% in axillary metastasis (4). Fluorodeoxyglucose (FDG) PET, which has an important role in investigating metastasis of malign tumors, has various detection rates in primary unknown tumors (PUT) with the most common being lung (5) and head and neck cancers of about 50%. There are studies supporting that FDG PET/CT is better in detecting primary tumors. In a study, a rate of 55% was reported for FDG PET/CT, whereas 31% for FDG PET in cervical lymph node enlarged patients (6, 7). In another meta-analysis, the detection rate of FDG PET/CT was 37% with the most common primary being lung (33%) (8). In another study, 28.5% of metastatic cases were unable to locate the primary foci using FDG PT/CT (9). In some centers, otorhinolaryngologists particularly use routine PET/CT for lymph node enlargements in the head and neck region (10).

The limitations of radiological methods redirect clinicians to pathological evaluation. Because many different targeted drugs were being used for different tumor types, finding the exact primary focus of the metastatic tumors is necessary in oncology practice. One of the most definitive results may be accomplished by a histological examination.

The histopathological assessment of excisional lymph node biopsies is cost effective in patients with metastatic lymph nodes and who were being investigated for primary tumors. In these patients, the tumor can only be diagnosed by the histopathological evaluation of the enlarged lymph node, which also excludes hematological malignancies (11). These excisional biopsies may be the only way for determining treatment protocols and prevent patients from more invasive procedures.

Tru-cut, incisional, or open biopsy can provide material for histopathological evaluation; however, total excision of the lymph node with intact capsule is the gold standard for pathological analysis (1). FNAB is relatively useful for epithelial tumors, but excisional biopsies are more important as they enable better samples for tumor morphology as well as IHC and histochemical analysis (12). As epithelial tumors metastasize lymph nodes from subcapsular sinuses, total excision with intact capsule is much more important for pathological evaluation. However, lymph node excision is a procedure and we know that every operation has its own risks due to anesthesia or the procedure itself. Therefore, the decision for lymph node excision should be considered based on all the aspects of the patient.

As the most common subtypes of PUT are unspecified adenocarcinomas, undifferentiated adenocarcinomas, and poorly-differentiated tumors, it is very important to specify the primary focus of the metastatic disease. The general pathological algorithmic approach for differentiating metastasis is to decide whether the tumor is epithelial, lymphoid, sarcomatous, or melanoma. Although there is no worldwide accepted guidelines for pathological analysis, it is commonly advisable to start with vimentin, Cluster of Differentiation (CD) 45, HMB-45, and pancytokeratin (2, 13, 14). Many and different antibodies can be used for IHC; however, sometimes overlapping results may complicate suggestions for primary tumors. In cases with a general impact of epithelial tumor metastasis, CK 7 and CK 20 may be chosen as the first step (15). In all of our cases, the diagnostic approach was initiated with pancytokeratin, vimentin, and CD45 to decide the nature of the tumor.

Antibodies specific for an organ or a tumor type can be added due to histological findings (such as PLAP and OCT ¾ for germ cell tumors; chromogranin A, synaptophysin, and CD 56 for neuroendocrine tumors; PSA and PSAP for prostatic origin; mammoglobin and GCDFP-15 for breast origin; CDX2 for intestinal origin; WT1 and CA-125 for ovarian cancers; TTF-1 for lung and thyroid cancer; and thyroglobulin for thyroid origin). Despite the fact that all tumor types may not have a definite specific antibody, IHC analysis is advantageous among many imaging methods due to its cost-effectiveness (2, 12, 16). We also used specific antibodies, such as thyroglobulin, CA125, CD X2, WT1, and GCDFP15, for detecting the primary foci.

The necessity for molecular diagnostic methods cannot be denied because gene expression profiles have an important role in tumor classification according to literature (17, 18) However, the accessibility to gene profiling methods can be impossible for small scale hospitals and this impossibility increases the importance of histopathological evaluation and IHC analysis of the excisional biopsies in especially small centers.

Even by using many diagnostic modalities, some of the metastatic cases remain as primary unknown tumors, forming the fourth most common cause of death (1).

The first-step diagnostic approach must include IHC markers that may help to decide if the tumor is epithelial, sarcomatous, lymphoid, or melanoma. In cases of melanoma and germ cell tumors, it is important to remember that the primary tumor can be "burnout". The diagnosis of the primary tumor from the histopathological evaluation is important for clinical, prognostic, and treatment protocols especially for tumors of which primary focus can be regressed spontaneously. As observed from our results, melanoma is the most common metastatic tumor with unknown primary focus. In 6 cases (28.5%), melanoma was diagnosed due to its metastasis.

Molecular DNA profile studies added to pathological evaluation increases the diagnostic rate up to 80%. However, the high cost and inapplicability of molecular studies at every center emphasize the accessibility and cost effectiveness of routine pathological examination and IHC analysis.

CONCLUSION

Nonhematological malignancies presenting with LAP are one of the most complicated cases for clinicians. In cases presenting with LAP without a primary focus found by simple radiological methods, the primary tumor can be diagnosed by a histopathological evaluation of the metastatic lymph nodes. The histopathological evaluation of the excisional metastatic lymph node biopsies is an important method due to cost effectiveness and easy applicability.

Ethics Committee Approval: Not required in this study.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.D., S.E., V.K.; Design - Y.D., Ö.İ.Ç., S.Y.Ç.; Supervision - Ö.D., S.Y.Ç.; Resource - Y.D., Ö.D., V.K.; Materials - V.K., Ö.D.; Data Collection and/or Processing - Y.D., Ö.D., S.E., V.K., Ö.İ.Ç., S.Y.Ç.; Analysis and/or Interpretation - Y.D., S.E., S.Y.Ç., Ö.İ.Ç.; Literature Search - Ö.D., V.K., S.Y.Ç.; Writing Manuscript - Y.D., Ö.İ.Ç., S.Y.Ç., S.E.; Critical Reviews - V.K., Ö.İ.Ç., S.Y.Ç.; Other - Y.D., S.E., Ö.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 137-139
DOI: 10.5152/turkjsurg.2017.3206

Case Report

Missed thyroid gland after total thyroidectomy

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ABSTRACT

Missed gland is an extremely rare condition. It is a mediastinal thyroid mass found after total thyroidectomy. We report a case of missed gland. The patient underwent total thyroidectomy due to multinodular goiter and thyroid stimulating hormone levels did not increase after surgery. Pathological tests revealed a micropapillary carcinoma. Thyroid ultrasonography and scintigraphy scan revealed mediastinal thyroid mass. The patient underwent redo surgery without sternotomy and there was no morbidity after the second surgical procedure. Most missed thyroid gland cases are due to incomplete removal of plunging thyroid goiter during total thyroidectomy. They also can be attributed to a concomitant, unrecognized mediastinal goiter, which is not connected to the thyroid gland with vessels or a thin fibrous band. It should be noted that absence of signs like mediastinal mass or tracheal deviation in preoperative chest X-ray does not exclude substernal goiter. The presence of a missed thyroid gland should be kept in mind when postoperative thyroid stimulating hormone levels remain unchanged.

Keywords: Missed thyroid gland, retrosternal goiter, substernal goiter, total thyroidectomy

INTRODUCTION

"Missed gland" is the substernal portion of thyroid that can be defined as thyroid formation with cervical departure that goes beyond the superior thoracic strait for at least 3 cm and is connected to the cervical portion of thyroid with or without a thin fibrous band or vascular structure, which is forgotten after total thyroidectomy (1, 2).

Missed thyroid gland should be differentiated from autonomous intrathoracic goiter (AIG), which is a thyroid gland formation located in the thorax or the mediastinum, has no parenchymatous or vascular connections with the cervical thyroid gland, and is fed by thoracic vessels. AIG is caused by abnormal embryonic development of the thyroid gland and must be distinguished from migratory goiters or missed thyroid gland after surgery. Here, we report a patient who previously underwent total thyroidectomy with "missed thyroid gland" in the mediastinum.

CASE PRESENTATION

The patient was a 58-year-old female, who underwent total thyroidectomy for multinodular goiter at our hospital (Figure 1). Thyroid function tests and TSH levels were normal before the first surgery. The thyroid ultrasonography (USG) showed multiple nodules in both lobes, and chest X-ray was insignificant. Thyroid scintigraphy scan was omitted due to normal thyroid function tests. Pathological tests revealed a 0.4-cm micropapillary carcinoma without a thyroid capsule involvement. Radioactive iodine (RAI) treatment was not required. Following the surgery, TSH levels did not increase (4.7 mIU/L) without levothyroxine replacement. Postoperative USG showed 25×24×24 mm hypoechoic thyroid gland inferior to the left thyroid lobe with a 10-mm hypoechoic nodule, which was confirmed with a thyroid scintigraphy scan (Figure 2) as a low activity nodular lesion. Fine-needle aspiration (FNA) biopsy revealed a follicular lesion. Surgery was planned and the missed gland was removed without sternotomy through a cervicotomy (Figure 3, 4). The patient was discharged one day after the surgery with no postoperative morbidity. A written informed consent obtained from the patient.

DISCUSSION

If total thyroidectomy is to be conducted, it is of vital importance conduct the operation efficiently and safely. Total thyroidectomy is described as resection of whole thyroid tissue to avoid recurrence (3). "Missed thyroid gland" is an extremely rare condition, which is defined as the appearance of a mediastinal thyroid mass after total thyroidectomy (1, 4, 5). In majority of the cases, missed gland is a result of incomplete removal of a plunging goiter, although sometimes it may be attributed to a concomitant,

Cite this paper as:
Abdulrahman SM, Teksöz S, Ferahman S, Demiryas S, Bükey Y, Özyiğin A. Missed thyroid gland after total thyroidectomy. Turk J Surg 2018; 34: 137-139.

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Received: 17.05.2015
Accepted: 29.07.2015
Available Online Date: 03.01.2018

Available online at
www.turkjsurg.com

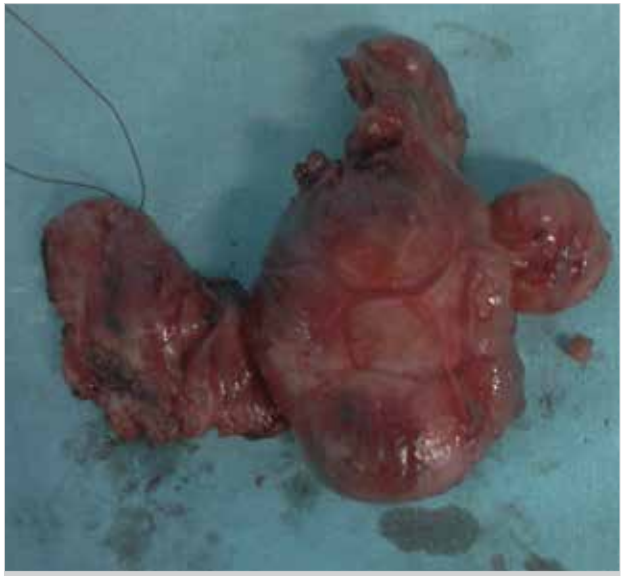

Figure 1. Total thyroidectomy (20.12.2012)

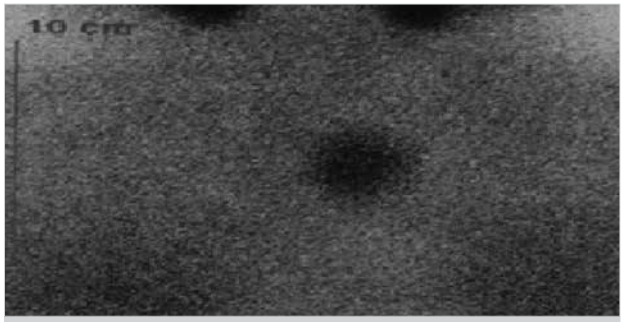

Figure 2. Postoperative scintigraphy: Arrow shows postoperative missed gland (05.08.2014)

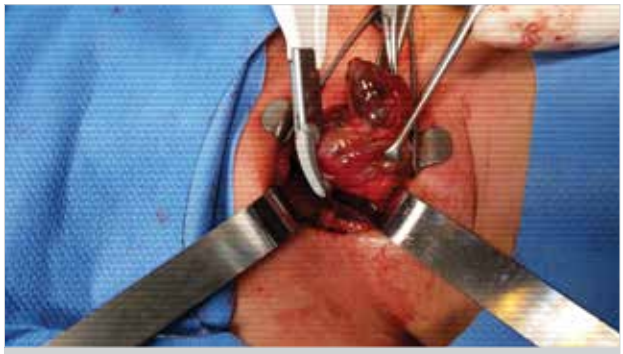

Figure 3. Removal of missed gland (24.11.2014)

unrecognized mediastinal goiter, which is not connected to the thyroid (4). The most frequent recurrence areas that are associated with embryologic location after total thyroidectomy also stand out as anatomical problems. These are pyramidal lobe and thyrothymic and zuckerkandl remnants (3).

There was a rest tissue present in our case at the thyrothymic location. Our case matches 4th grade according to Sacket et al. (6) classification. Also, according to Sacket et al. (6) classification, rest tissues can be missed during total thyroidectomy due to the permanence between thyroid tissue and the 3rd and 4th grade remnants, which constitute 20% of the remnants. It can be prevented if particular attention is paid to preoperative imaging and intraoperative management during the first operation (2, 7). Thus, routine dissection of pretracheal area and seeing thymus in the thoracic inlet should be a part of every total thyroidectomy that is performed due to nodular goiter. The remnants that underwent nodular change can be frequently palpated during surgery. Retrosternal recurrence can be triggered this kind of thyroid tissue is not dissected completely and this situation may cause patients to face an increased risk of a potential sternotomy need later (3).

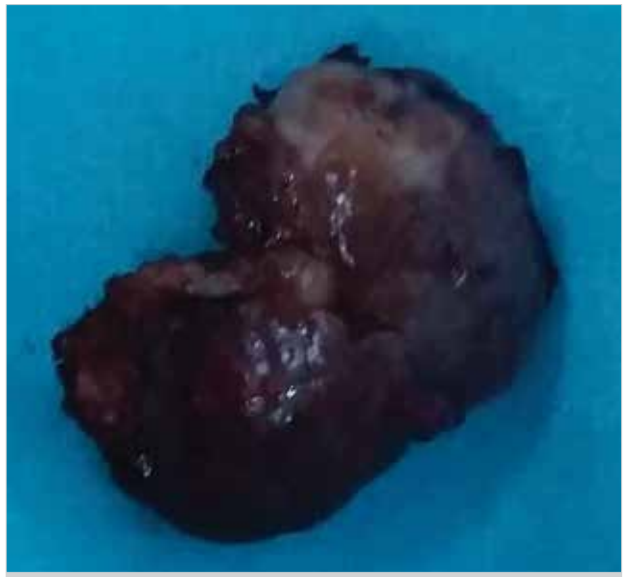

Figure 4. The specimen of missed gland (24.11.2014)

A substernal goiter has been defined as an enlarged gland with extension down to the aortic arch with its lower border reaching the transverse process of the 4th thoracic vertebra or below, or with greater than 50% of the goiter volume present behind the sternum (2). Its incidence varies between 1.7% and 30% of all goiters (8). A retrosternal goiter (RG) is commonly defined as having most of its mass in the mediastinum. RG incidence rates range between 2% and 50% of all goiters, depending on the definition (9, 10). Majority of the patients are asymptomatic, with their goiters detected incidentally during radiologic examinations. Routine chest radiographs seldom miss a mediastinal mass. RG should be suspected if the lower poles cannot be palpated on physical examination (9-11). In our case, there was no symptom due to the remaining thyroid mass in the mediastinum. We did not palpate any mass beneath the thyroid gland extending to the mediastinum during the first operation. As there was no hyperthyroidism prior to the first operation, scintigraphy was omitted. USG and chest X-ray did not show RG and consequently retrosternal area exploration was not performed.

Mediastinal extension is missed during cervical exploration because mediastinal portion of RGs is connected to the cervical part with a thin fibrous band. Absence of mediastinal mass or tracheal deviation in preoperative chest X-ray results in retrosternal area exploration in such cases being omitted (1, 2).

Missed gland is a rare pathology; when postoperative TSH levels remain unchanged missed gland should be suspected; however, surgical treatment for missed gland is associated with low morbidity when performed at specialized centers.

CONCLUSION

The presence of a missed thyroid gland should be kept in mind when postoperative TSH levels remain unchanged after a total thyroidectomy.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.M.A.; Design -S.F.; Supervision - S.T.; Resource - S.M.A.; Materials - S.M.A.; Data Collection and/or Processing -S.F.; Analysis and/or Interpretation -S.T.; Literature Search - S.D.; Writing Manuscript - S.M.A.; Critical Reviews - Y.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 140-142
DOI: 10.5152/UCD.2016.3214

Case Report

Regression in local recurrence in the contralateral breast following mastectomy in bilateral locally advanced breast cancer: A comparison of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios

Abdullah Durhan[1], Gamze Durhan[2], Aydan Eroğlu[1]

ABSTRACT

The neutrophil-to-lymphocyte ratio is clinically accepted as a marker of systemic inflammatory response. In breast cancer patients, neutrophil-to-lymphocyte ratio can be used as an important prognostic indicator of survival. In routine laboratory tests, the platelet-to-lymphocyte ratio can also be examined in addition to neutrophil-to-lymphocyte ratio. Although the effects on breast cancer survival of platelet-to-lymphocyte ratio, which is accepted as the twin of neutrophil-to-lymphocyte ratio, are not as widely accepted as those of neutrophil-to-lymphocyte ratio, platelet activation is known to be a feature of cancer. Here, we present the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio of a patient with locally advanced cancer of the left breast who underwent a simple mastectomy that reduced the tumor load. Following surgical therapy, a remarkable regression was observed in the local recurrence area of the right mastectomy site; at the same time, the patient's neutrophil-to-lymphocyte ratio and PLR values significantly decreased.

Keywords: Locally advanced stage, breast cancer, simple mastectomy, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

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Cite this paper as:
Durhan A, Durhan G, Eroğlu A. Regression in local recurrence in the contralateral breast following mastectomy in bilateral locally advanced breast cancer: a comparison of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios. Turk J Surg 2018; 34: 140-142.

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Received: 23.05.2015
Accepted: 04.08.2015
Available Online Date: 03.01.2018

Available online at
www.turkjsurg.com

INTRODUCTION

Breast cancer is the most commonly observed type of cancer in women; in approximately 25%-30% of patients, diagnosis is made when the breast cancer is locally advanced (1). As in other cancers, the inflammatory response in breast cancer plays an important role in cancer development. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which can be obtained from a peripheral full blood count, are routinely clinically accepted as markers of systemic inflammatory response (2, 3). Recent studies have shown that the immune response increases with a reduction in tumor load (4). Here, we present the NLR and PLR of a patient with locally advanced breast cancer who underwent simple mastectomy that reduced the tumor load.

CASE PRESENTATION

A 52-year-old woman was referred to our clinic for surgical treatment of locally advanced breast cancer. From the patient's history, it was learned that one year previously, she had presented at another center with the complaint of a mass causing color change and rash bilaterally on the breasts. The patient was diagnosed with Grade 3 invasive ductal carcinoma breast cancer on the right side. Estrogen receptor (ER) and progesterone receptor (PR) tests were strongly positive, and HER2 expression was negative (luminal A tumor). She was administered eight cycles of neoadjuvant chemotherapy, and simple mastectomy was performed on the right breast followed by hormonotherapy. It is not known why the patient underwent mastectomy of only the right breast instead of a bilateral mastectomy at the other hospital. She applied to our clinic due to increased symptoms in her left breast. When the patient presented at our clinic, the mass in her left breast had grown, there was increased rash on the breast skin, and a new mass had developed on the incision scar of the right side of the mastectomy area.

In the physical examination, multiple nodular metastatic masses, the largest of which was 1 cm in diameter, were detected on the incision scar of the mastectomy site of the right breast along with fixed lymphadenopathies in the right axilla. The left breast was completely full of tumoral mass, with tumor invasions of the skin. Inflammatory appearance of the skin, satellite nodules, and fixed lymphadenopathies in the left axilla were observed. The preoperative images are shown in Figure 1.

No abnormal findings were seen in the PA pulmonary radiograph, abdominal pelvic ultrasonograph (USG), or bone scintigraph. No pathology was determined by routine biochemistry. The patient was informed, and a simple mastectomy was applied to the left breast to reduce the tumor load. As the skin was completely covered with the tumor, the skin borders close to the sternum could not be approached with the primary incision; after removal of the breast, which was infected and had tumor necrosis, sec-

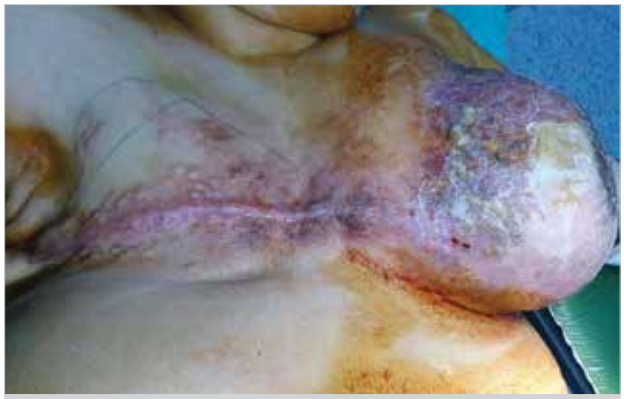

Figure 1. Preoperative image. The left breast was completely full of tumoral mass, with tumor invasions of the skin. An inflammatory appearance of the skin and satellite nodules were observed

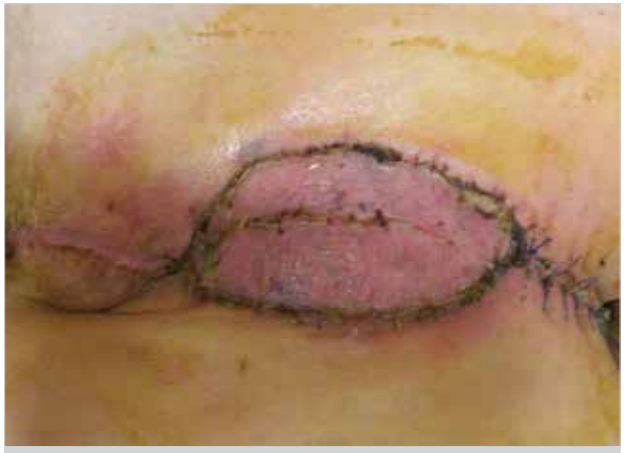

Figure 2. The healed left side graft area and the regression of local recurrences on the right side

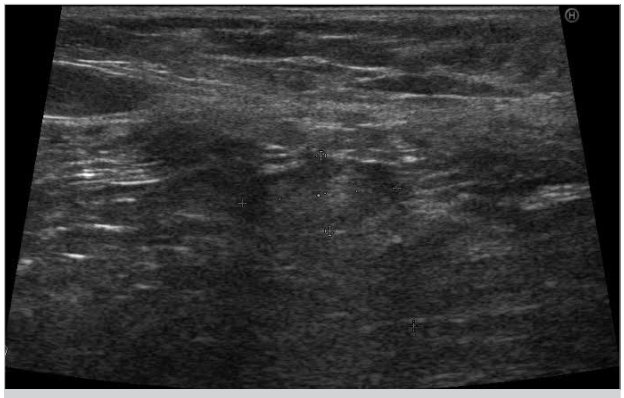

Figure 3. Axillary lymph node with thin cortex and hyperechogenic fatty hilus was demonstrated in ultrasound images

ondary healing was applied. After 10 days, as the granulation tissue was seen to be sufficient, the open wound was repaired with graft application. No postoperative complications developed, and the patient was discharged on postoperative day 7. After removal of the tumor load in the left breast, a regression in local recurrence sites in the right mastectomy area was observed. The healed left side graft area and the regression of local recurrences on the right side are shown in Figure 2. In addition, the preoperative axillary fixed lymphadenopathies were determined to have receded on physical examination and USG imaging, and the lymph nodes were observed to have replaced the thin cortex with a hyperechogenic fatty hilus (Figure 3).

In the histopathological examination of the specimen, a Grade 3 (Scarf Bloom Richardson) invasive ductal carcinoma 11 cm in diameter was determined. There were perineural and lymphovascular invasions, many satellite tumor nodules around the tumor that had led to ulceration and an appearance of infiltration to the epidermis and breast head/areola, continuation of the tumor with a deep surgical border, and infiltration to the striated muscle in this area. ER was determined as 80%, PR as 5% positive and c-erb B-2 as negative. In the postoperative period, aromatase inhibitor was administered. The results of consecutive complete blood tests showed that the NLR and PLR values of 7.05 (N: 84%, L:11.9%), and 407.5 (P: 326, L: 0.8×10^9/L), respectively, on preoperative Day 1 decreased to 4.35 (N: 74%, L: 17%) and 380 (P: 266, L: 0.7×10^9/L), respectively, on postoperative Day 5 and to 2.63 (N: 65.2%, L: 24.7%) and 251 (P: 277, L: 1.1×10^9/L), respectively, on postoperative Day 14.

Written informed consent was obtained from the patient who participated in this case.

DISCUSSION

In cancer patients, the clinical prognosis is as much related to the properties of the tumor as to the patient's response to the tumor (5). In recent studies, cancer and immunology have become increasingly important. For many years, immunologists have stated that the immune response is suppressed in cancer patients and the response to the tumor is reduced (6). Especially in patients with excessive tumor loads, there is evident immune suppression; with reduction of the tumor load with primary surgery, the immune response has been seen to increase. This is explained by changes occurring in T-cells including increase of antitumor responses with the reduction in tumor load (4).

Neutrophil-to-lymphocyte ratio, which can be obtained from a peripheral full blood count, is a routine clinical marker of systemic inflammatory response (2, 3). Increased peripheral neutrophils before treatment and decreased lymphocyte count have been shown to have negative effects on the survival of cancer patients (7). In addition, it has been found that just as increased neutrophil numbers are related to the paraneoplastic activity of the tumor, reduced lymphocyte numbers are related to suppression of the immune system. While neutrophils, which affect tumor growth, are the main source of angiogenesis and growth factors, lymphocytes form the patient immune response with cytotoxic cell death and production of cytotoxin, which prevent proliferation of tumor cells (8). Increased NLR in breast cancer has been shown to have increased mortality (2). In addition, in a recent study, high NLR in breast cancer patients was found to be related to lymph node metastasis (3).

Although the effects of NLR on survival in breast cancer have been widely accepted as a prognostic factor, there are few studies supporting the use of PLR as an independent prognostic factor. However, experimental studies and clinical data have shown that platelet activation is a feature of cancer, with support of neoangiogenesis, destruction of the extracellular

matrix, and expression of adhesion molecules and growth factors (9). Seeretis et al. (10) determined a relationship between increased PLR and metastatic lymph nodes in cancer patients.

In the case presented here, the tumor load was reduced with a simple mastectomy. When the blood values of the patient were examined during this procedure, a continuous reduction in NLR was recorded together with the reduction in tumor load. The regression observed in the masses in the chest wall of the patient can be related to the decrease in the NLR value. Even though no absolute relationship has yet been shown between PLR and breast cancer, the regression of the tumor in this case together with decreased PLR values suggests that PLR can be effective in tumor prognosis.

CONCLUSION

In patients with locally advanced breast cancer, decreases in NLR and PLR values parallel to the reduction of tumor load with surgery may cause an increase in immune response and regression of the tumor. Further studies with an extensive series are required to better understand this relationship.

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

Peer-review: Externally peer-reviewed.

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

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 143-145
DOI: 10.5152/turkjsurg.2017.3199

Case Report

An incidental giant preperitoneal fibrolipoma diagnosed during laparoscopic cholecystectomy

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ABSTRACT

Preperitoneal lipomas are rare in clinical practice. Here we report an unexpected diagnosis of a giant preperitoneal fibrolipoma detected intraoperatively during laparoscopic cholecystectomy in a 56-year-old woman. The mass was excised and a histopathological examination confirmed fibrolipoma. No recurrence was found on follow-up. In the literature, there have been many cases with unexpected diagnoses during laparoscopy. Here, we present an incidental giant preperitoneal fibrolipoma, which was overlooked by ultrasound and physical examination, but was detected during laparoscopic cholecystectomy.

Keywords: Giant lipoma, preperitoneum, diagnostic errors, laparoscopy

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Cite this paper as:
Başak F, Hasbahçeci M, Canbak T, Yücel M, Acar A, Şişik A, Baş G, Karabulut MH, Kır G. An incidental giant preperitoneal fibrolipoma diagnosed during laparoscopic cholecystectomy. Turk J Surg 2018; 34: 143-145.

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Received: 12.05.2015
Accepted: 04.08.2015
Available Online Date: 03.01.2018

Available online at
www.turkjsurg.com

INTRODUCTION

Lipomas as the most common form of soft tissue tumors are benign lesions composed of adipose tissue. Although these tumors are frequently observed elsewhere on the body, they are rare in thoracic and abdominal cavity (i.e., small and large bowel) and in preperitoneal area (1-4). Although many lipomas are <1 cm in diameter, they can grow up to >6 cm in diameter. Masses with massive size can cause pressure on adjacent anatomical structures and result in symptoms. Some sources claim that malignant transformation may occur, whether others say that this has yet to be convincingly documented (1, 2). Lipomas are classified into various subtypes according to histopathological features, including fibrolipoma, myxolipoma, chondroid lipoma, and myolipoma. The literature contains case reports about preperitoneal lipomas and preperitoneal lipoleiomyoma. Fibrolipomas are known to occur at many various locations such as the esophagus, nerves, oral cavity, spermatic cord, and retroperitoneum (5). Preperitoneal fibrolipoma are exceptionally rare; to the best of our knowledge, this is the first case reported.

In this study, we present a case of a giant preperitoneal fibrolipoma that was missed with routine imaging modalities and physical examination and was incidentally diagnosed during laparoscopic cholecystectomy.

CASE PRESENTATION

A 56-year-old woman was admitted with abdominal discomfort and pain. Medical evaluation included physical examination, blood tests, and ultrasound focused on the hepatobiliary system. All were normal except a sonographic diagnosis of cholelithiasis. The patient's body mass index was 31 kg/m^2. The patient underwent surgery for cholelithiasis. Laparoscopy was performed via the open entrance method at midline below the umbilicus. A 360° exploration of the abdomen revealed a giant mass with a diameter of 16 cm. The mass was found protruding into the abdomen near the umbilical trocar entry. It was regarded as a lobulated preperitoneal lipoma due to its macroscopic appearance (Figure 1). First, the mass was carefully excised via open surgery (midline incision under the umbilicus) so as to not shatter it. Midline incision was closed except the trocar area. Then, additional trocars were placed, and standard laparoscopic cholecystectomy was performed uneventfully.

Gross examination of the specimen revealed a firm, rubbery mass, which was encapsulated by a smooth surface, weighed 750 g, and measured 16 cm in diameter. On pathological examination, all cellular components of the tumor including adipocytes, fibroblasts, and vascular elements appeared benign. There were no signs of cellular atypia, increased mitotic activity, or necrosis. Immunohistochemical staining was positive for S-100 at mature adipocytes and negative for desmin and smooth muscle actin in the fibromatous areas (Figure 2). The patient was discharged at first postoperative day uneventfully. No recurrence or relapse occurred at the 6-month follow-up.

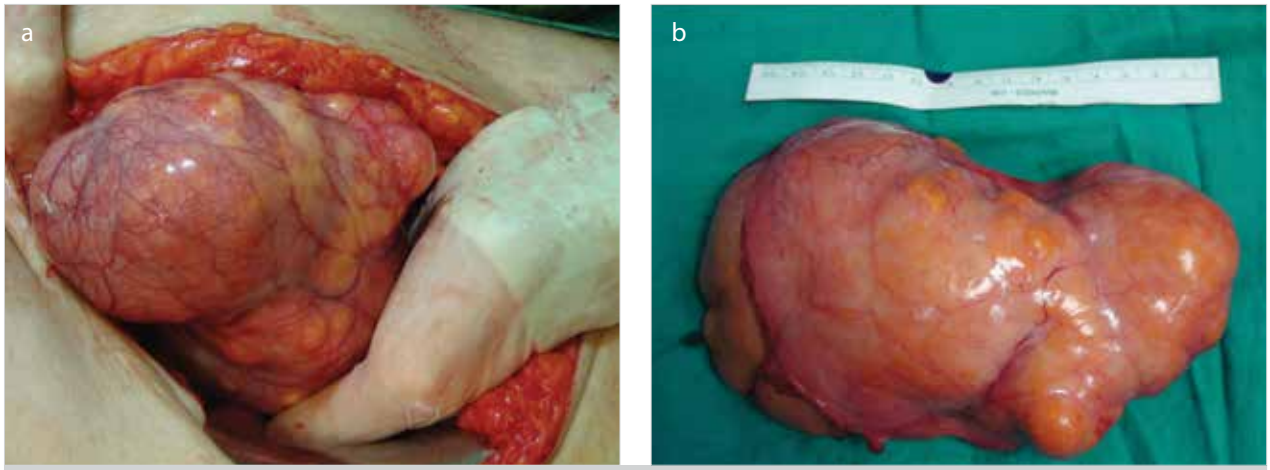

Figure 1. a, b. A surgical view; (a) Intraoperative view of mass, (b) Excised specimen

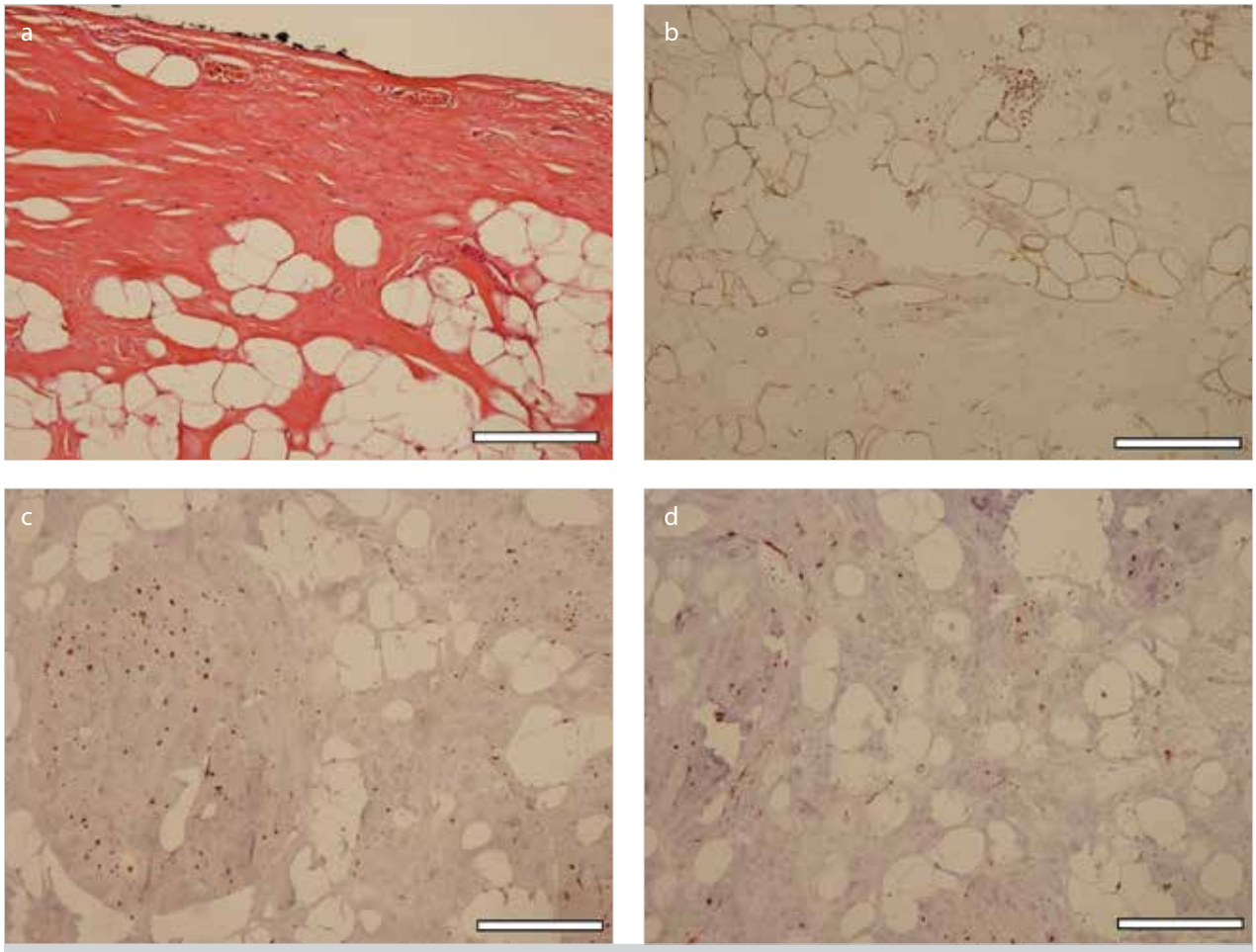

Figure 2. a-d. Microscopic imaging of specimen with different methods; (a) H/E ×200, (b) S-100 ×200, (c) Desmin ×200, (d) SMA ×200, Scale bar: 100 µm

DISCUSSION

Lipomas are benign adipose tissue tumors. The etiology is not clear and is known to be both sporadic and inherited. Fibrolipomas are one of the less common histological subtypes of lipoma and have significant fibrous components mixed with fat lobules (1, 6). Although a possible relationship between obesity and lipoma occurrence is suspected, it has not yet been proven (7).

Fibrolipomas are benign lesions. In the literature, recurrences and malignant transformations have been reported. There is a controversy regarding whether giant lipomas (i.e., in particular those >10 cm or weighing >1000 g) are typical lipomas or liposarcomas. Rapidly growing lipomas of >10 cm in size should be considered as possible liposarcomas. Depending on their locations, they may cause intestinal obstruction (5). In the present case, although the mass was 16 cm in diameter,

intestinal obstruction at admission was not seen due to its preperitoneal localization.

Management and prognosis of fibrolipomas do not differ from other forms of lipomas. The choice of treatment is complete surgical excision. Although the surgery is curative in most cases, postoperative follow-up is also recommended (1, 5). Besides the absence of sarcomatous malignant transformation at histology and prominent lipomatous lesions over the body, the present case was admitted to a follow-up program due to the diameter of the mass. However, life-long follow-up may not be considered for patients with similar findings due to cost-effectiveness.

In the literature, various cases of incidental findings during laparoscopy have been reported. These intra-abdominal lesions include liver metastasis, gastric cancer, stromal tumor of the small bowel, pancreatic cancer, and mucocele of the appendix (8). In the present case, we detected a giant mass located near the umbilicus via a 360° abdominal exploration during laparoscopic cholecystectomy.

Although complete abdominal exploration during laparoscopic cholecystectomy was questioned in the literature, it is generally recommended to perform this exploration to lower the chance of missed malignancies after laparoscopy (9-11). Missed diagnosis in ultrasound is another challenging problem (12). Furthermore, the use of hepatobiliary ultrasound for the diagnosis of cholelithiasis in an obese patient might cause such problems as in this case. Although additional imaging has not been regarded as the routine practice before laparoscopic cholecystectomy for all cholelithiasis cases, discordance between symptomatology and physical examination should warn physicians to perform detailed radiological examination.

CONCLUSION

360° surgical exploration for major pathologies can be accepted as the routine practice during laparoscopy. Preperitoneal fibrolipoma is a rare condition and can be found incidentally. Complete surgical excision is the choice of treatment. Because of the risk of recurrences and malignant transformations, careful postoperative follow-up is recommended, especially for giant lipomas.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.B., M.H.; Design - F.B., M.H.; Supervision - F.B., M.H., T.C., M.Y., Data Collection and/or Processing - F.B., M.H., T.C., M.Y., A.A., A.Ş., G.B., M.H.K., G.K.; Analysis and/or Interpretation - F.B., M.H., T.C., M.Y., A.A., A.Ş., G.B., M.H.K., G.K.; Literature Search - F.B., M.H., T.C., M.Y., A.A., A.Ş., G.B., M.H.K., G.K.; Writing Manuscript - F.B., M.H., T.C., M.Y.; Critical Reviews - A.Ş., G.B., M.H.K., G.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 146-148
DOI: 10.5152/turkjsurg.2017.3141

Case Report

Adrenal angiosarcoma

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ABSTRACT

Adrenal angiosarcoma is an uncommon neoplasm that derives from the vascular endothelium; due to its biological behavior, it should be distinguished from other adrenal tumors. We herein report a case of a 57-year-old woman with diagnosis of an adrenal tumor that was suspected to be malignant. The specimen was histopathologically proved to be an angiosarcoma. The patient was suffering from right upper quadrant pain; after laboratory and radiological workup, a non-functioning right adrenal mass, 14 cm in size, was recognized. A right subcostal incision was made, and adrenalectomy was performed successfully with tumor-free surgical margins. Two months after the operation, a positron emission tomography-computed tomography scan was ordered for follow-up. No tumor tissue or any other metastatic foci remained. The patient had been referred to our medical oncology department and underwent retroperitoneal radiotherapy. However, unfortunately, the patient died due to cardiac insufficiency during the follow-up period.

Keywords: Adrenal angiosarcoma, adrenal gland, malignant vascular tumors, adrenal incidentaloma

INTRODUCTION

Adrenal angiosarcomas are infrequently encountered neoplasms in daily practice; therefore, they are not well documented in the literature. The etiological factors of this neoplasm are still not clearly understood; however, in a case report, exposure to some carcinogens was believed to be the cause of an adrenal angiosarcoma. There is no evidence supporting the relationship between primary adrenal angiosarcoma and multiple neuroendocrine tumors. Also, administration of radiation therapy in the past or previous abdominal traumas has no correlation with adrenal angiosarcoma (1). In most cases, adrenal angiosarcomas are diagnosed coincidentally following routine workup for patient complaints, which are generally non-specific abdominal discomfort or pain (2, 3). In this report, we present a new case of adrenal gland angiosarcoma of unusual size, which will enrich the collected scientific data on this very rare clinical entity.

CASE PRESENTATION

A 57-year-old female patient with right upper abdominal pain was admitted to our hospital. Her past medical history included hypertension and hypercholesterolemia, which were under control. On physical examination, slight tenderness was found in the right upper quadrant, without any rebound or Murphy's sign. Cholecystitis was one of our differential diagnoses; therefore, the patient underwent abdominal ultrasound (US). Multiple gallstones were detected; however, significantly, a 14-cm abdominal lesion was also recognized beneath the liver. Therefore, computed tomography (CT) scans of the abdomen (Figure 1) and chest were ordered. A heterogeneous mass 14×12 cm in diameter, originating from the right adrenal gland, was revealed without contrast dying. There were no additional metastatic disseminations. Blood and urinary analyses documented no hormonal activity of the tumor. Preoperative LDH measurement was 422 U/L, VMA was 1.93 mg/day, normetanephrine was 255.5 µg/24 h, metanephrine was 60.9 µg/24 h, and cortisone was 2.03 µg/dL. There were no other significant results in the patient's biochemical or complete blood count workup. Because of the size of the tumor and its malignant potential, an open surgical procedure with right sub-costal incision was decided upon. Through a retroperitoneal approach, the solid mass, which was 15×10 cm in diameter, was dissected, and its bandings to the liver and right kidney were also freed using LigaSure. The mass had a highly vascular, solid appearance and was infiltrating the liver and its surrounding fatty tissues. Cholecystectomy and right adrenalectomy were performed together. The histopathological report that was acquired for the cholecystectomy material indicated chronic cholecystitis with multiple cholelithiasis. The adrenal tumor specimen was measured to be 16×10 cm with a weight of 886 grams (Figure 2). Histopathological examination showed that the tumor was an angiosarcoma containing hemorrhagic and necrotic areas that were infiltrating the adrenal cortex (Figure 3). The surgical boundaries were also reported as 2 mm distant to the tumoral lesion. Immunohistochemical study revealed that the tumor was expressing cluster of differentiation 31 (CD 31) (Figure 4).

Cite this paper as:
Cancan G, Teksöz S, Demiryas S, Özcan M, Bükey Y. Adrenal angiosarcoma. Turk J Surg 2018; 34: 146-148.

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Received: 16.03.2015
Accepted: 04.08.2015
Available Online Date: 03.01.2018

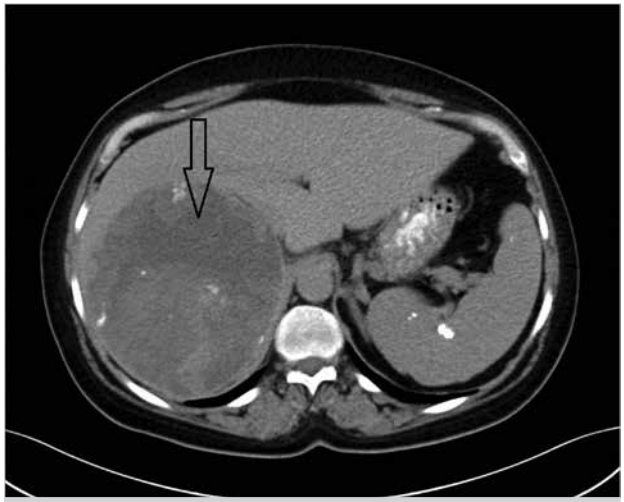

Figure 1. Computed tomographic images of the tumor

Figure 2. Macroscopic appearance of the tumor

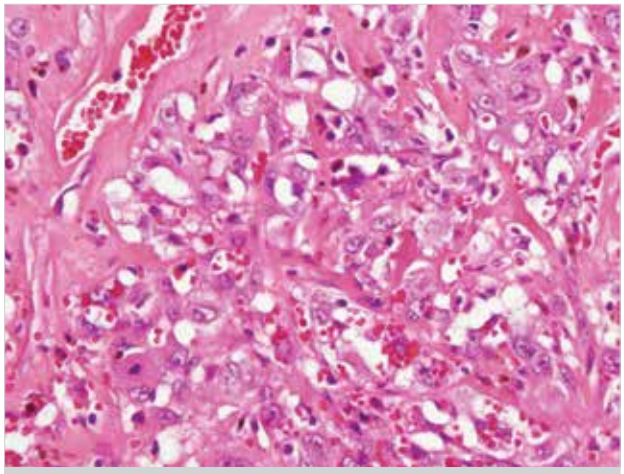

Figure 3. Vasoformative areas consisting of high grade epithelioid atypical endothelial cells (H&E ×400)

Postoperatively, the patient underwent medical oncology follow-up. Two months after the surgery, a whole body positron emission tomography-computed tomography (PET-CT) scan was performed; it showed no remaining tumoral tissue or any other metastatic foci (Figure 5). The tumor was large in size; retroperitoneally, it filled the upper right quadrant of the abdomen. Therefore, adjuvant radiotherapy was planned for the patient. She underwent a single dose of radiation therapy. In the 10th month of the postoperative period, the patient died due to cardiac insufficiency without any detected tumoral relapse. A written informed consent obtained from the patient.

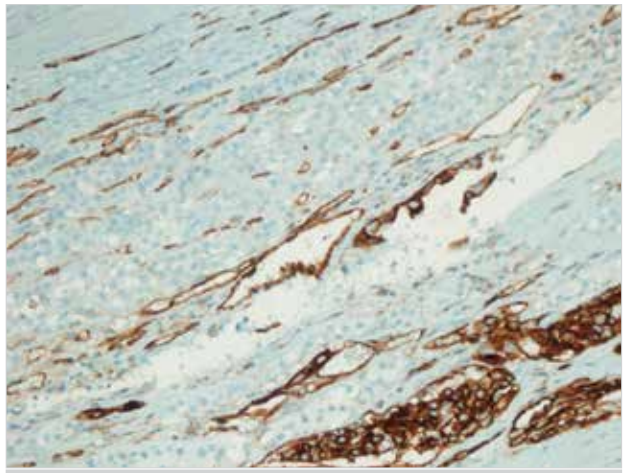

Figure 4. Tumoral cells expressing the typical vascular marker CD31 (CD31 ×200)

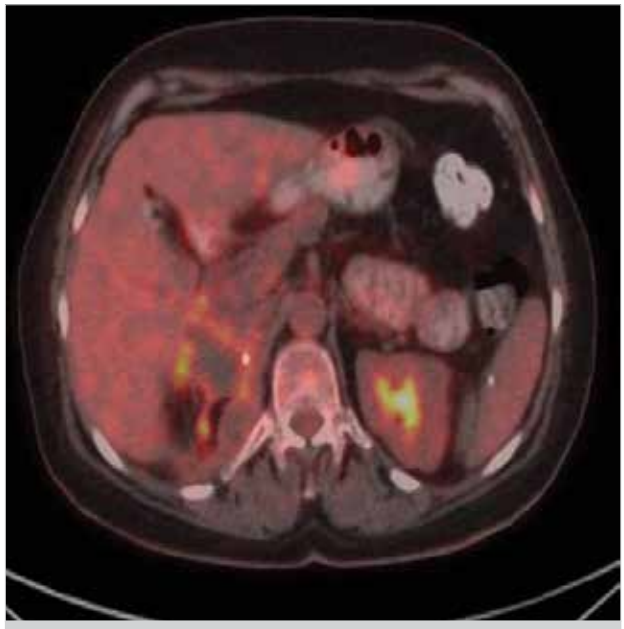

Figure 5. PET-CT scans of the patient after surgery

DISCUSSION

Angiosarcomas are very rare, malignant vascular tumors with high mortality rates (3, 4). Primary adrenal angiosarcoma is an especially rare entity that was first described by Kareti et al. (5) in 1988. Generally, the disease is predominant in males, is seen between the fourth and ninth decades, and presents with abdominal pain (2, 6). Radiologically, it is a heterogeneous mass whose size is greater than 5 cm. Also, the tumor usually expresses epitheloid histopathological findings (2, 7).

In this case, a right adrenal mass was recognized during an examination for biliary colic. The patient had neither a history of malignancy nor laboratory findings indicating any hormonal hyperfunctionality. Her hypertension was under medical control and was noted to be unrelated to her adrenal mass.

Regarding the optimal imaging method for adrenal masses, CT scan is the method of choice. In our case, a heterogeneous mass 14×12 cm in diameter adjacent to the inferior vena cava and the right renal vein was visualized in the CT scan; it was not dyed with contrast material (8, 9). The metastatic foci

were ruled out before the operation decision. Although the treatment modality for patients with adrenal angiosarcomas remains controversial, surgical eradication appears to have better outcomes (1). We also prefer open surgery with a right subcostal incision when malignancy is suspected. On the basis of the limited reports of adrenal angiosarcomas in the literature, surgery was combined with chemotherapy and radiotherapy. We did not choose a laparoscopic technique because it would not be adequate to resect a tumor of this size.

In the literature, the treatment modality of this rare case is described as controversial (1, 10). Due to limited experience with adrenal angiosarcomas, surgeons pursue different surgical extension procedures. According to the review by Stavridis et al. (11) some surgeons choose only adrenalectomy, while some add splenectomy or nephrectomy to adrenalectomy. The different surgical procedures are generally determined on the basis of the size and extension of the tumor. Also, postoperative chemotherapy and radiotherapy are chosen on the basis of the exhibited size and metastatic status of the tumor (11). In most cases, the neoplasms were reported to be well circumscribed and invasive, with a solid or cystic appearance (10). In this case, we encountered a highly vascular solid mass infiltrating the surrounding fatty tissue without any metastatic foci. Adrenal cortical carcinoma, pheochromocytoma, metastatic adenocarcinoma, or malignant melanoma should be distinguished from primary adrenal angiosarcoma (10). Benign neoplasms may simulate epitheloid angiosarcomas (10). Coincidence of functioning adrenal adenoma and primary adrenal angiosarcoma should also be considered (7). Endothelium-related markers (CD31, CD34, and Factor VIII antigen) usually aid differential diagnoses of malignant vascular tumors (8). The malignant cells were positively stained for CD31, CD34, and Ki67 (30%) in this case. Therefore, our case was reported as an epitheloid variant of angiosarcoma.

In the literature, only one adrenal angiosarcoma has been reported with a similar size to our case (3). Although angiosarcomas are known to have a very aggressive nature in tumor biology, primary adrenal involvement has a long survival time with complete resection margins (12).

The patient was discharged two days after the operation. Because we had resected the tumor with tumor-free surgical margins and no metastatic foci were found by PET-CT scan, adjuvant chemotherapy was not needed. However, because the tumor mass was resected and had occupied a significant volume in the retroperitoneal cavity, adjuvant radiotherapy was determined to be necessary for the patient.

As this is a very rare entity and knowledge of its biological behavior is limited, patient follow-up was planned to include routine laboratory tests and CT scans to keep us informed regarding the patient's future medical status and possible relapses. During the follow-up period, the patient died due to cardiac insufficiency.

CONCLUSION

Adrenal tumors may present with right upper abdominal pain. Appropriate radiological imaging techniques and laboratory findings can reveal this high-risk vascular adrenal pathology. Conventional open surgical techniques should not be overlooked when deciding how to treat unexpectedly large adrenal vascular tumors.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.C.; Design - S.T.; Supervision - Y.B.; Resource - S.D.; Materials -M.Ö.; Data Collection and/or Processing - G.C.; Analysis and/or Interpretation - S.T.; Literature Search - S.D.; Writing Manuscript - S.T.; Critical Reviews - Y.B., M.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 149-151
DOI: 10.5152/UCD.2017.3221

Case Report

Hyalinizing trabecular tumor of the thyroid gland

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ABSTRACT

Hyalinizing trabecular tumor was first described by Carney et al. (1) in 1987 and is a rare benign tumor of the thyroid gland that shares some of the microscopic features of medullary and papillary thyroid carcinoma. Hyalinizing trabecular tumor derives from follicular cells, and it is characterized by an apparent trabecular pattern and intratrabecular hyalinization. In this study, we present the case of a 40-year-old female patient with thyroid gland nodules, whose ultrasound results, clinical behavior, and fine-needle aspiration biopsy results were suspicious; the pathology after thyroidectomy indicated hyalinizing trabecular tumor. We aimed to show the role of clinical behavior, radiology, fine-needle aspiration, and histological and immunohistochemical analysis in the differential diagnosis of hyalinizing trabecular tumor. Hyalinizing trabecular tumor which can be confused with papillary and medullar carcinoma of the thyroid gland, is mostly benign but some malignant and metastatic cases have been reported. Therefore, diagnosis, treatment, and follow-up steps of Hyalinizing trabecular tumor should be planned in consideration of a malignant potential.

Keywords: Thyroid tumors, hyalinizing trabecular tumor, trabecular pattern

INTRODUCTION

Hyalinizing trabecular tumor (HTT) is a rare thyroid gland neoplasm that was first described in 1987 by Carney et al. (1). It is a thyroid tumor of a follicular origin and is characterized by trabecular pattern and intratrabecular hyalinization (2). HTT entered World Health Organization's (WHO) Thyroid Tumor Classification in 2004 (3). Cytological appearance of HTT is mostly confused with malignant lesions that need thyroidectomy and lymph node dissection. Several cytological and histologic features of HTT are identical to those of papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma. Some authors suggest that HTT is not a different type of thyroid carcinoma, but rather a variant of PTC. Preoperative cytological diagnosis is rarely accurate (4). Most cases are benign in nature; however, some HTT cases have been reported with lung and lymph node metastasis (5). Furthermore, microscopic appearance of HTT is similar to that of paraganglioma (5).

In this article, we will present the clinical and pathological features of HTT and focus on the differential diagnosis of a female patient who was recognized to have HTT after thyroidectomy.

CASE PRESENTATION

A 40-year-old female patient was admitted with difficulty in swallowing. The patient's thyroid ultrasound (US) result demonstrated a 15×9 mm heterogeneous hypoechoic solid nodule on right lobe of the thyroid gland. Fine-needle aspiration biopsy (FNAB) was performed. Cytological examination showed atypical epithelial cells with hypercellular and trabecular patterns around the nucleus and fine chromatin, and some cells had grooves. Result was inconclusive for occurrences of papillary carcinoma and medullary carcinoma.

Magnetic resonance imaging (MRI) results demonstrated a 12×10 mm T1A hypointense, T2A hypointense, well circumscribed nodule on the right lobe of the thyroid gland. For differential diagnosis of medullary carcinoma, MRI of the pituitary gland was performed and no pathological result was obtained. Patient was euthyroid. Free thyroxin (fT4) and thyroid stimulating hormone (TSH) levels were in normal range. Calcitonin value was normal for a female. Operation was decided on for the patient, and total thyroidectomy was performed. Postoperative pathological diagnosis was HTT of the thyroid gland.

Macroscopic examination on thyroidectomy: 1.2-cm diameter well circumscribed, regular, homogenous, yellow-colored, nodular lesion under the capsule of the right thyroid lobe. Results of the microscopic examination: the nodule forms a clear trabecular pattern and has extended polygonal cells that include the nuclear notch with pseudoinclusions in some places (Figure 1). There was stromal hya-

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Cite this paper as:
Ergün S, Akıncı O, Öztürk T, Karataş A. Hyalinizing trabecular tumor of the thyroid gland. Turk J Surg 2018; 34: 149-151.

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Received: 28.05.2015
Accepted: 10.08.2015
Available Online Date: 03.01.2018

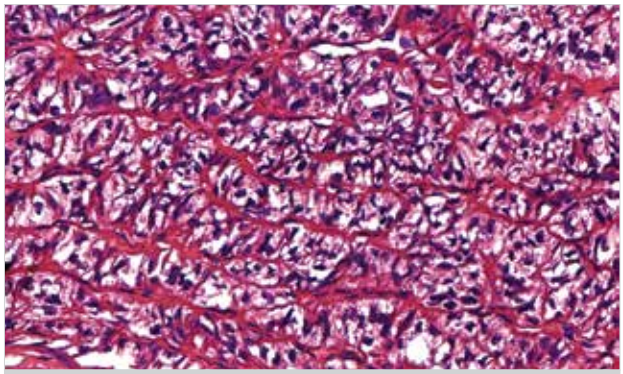

Figure 1. Tumor tissues with trabecular growth pattern (H&E; 400×)

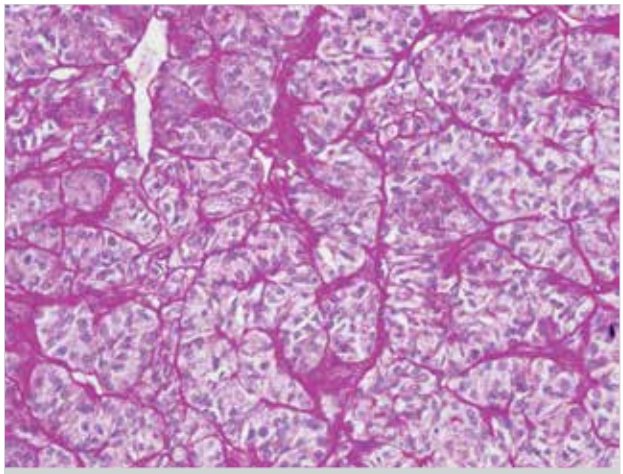

Figure 2. Stromal hyalinization with PAS (+) staining

linization between trabeculae. On histochemical examination, these hyalinized areas stained positive for Periodic acid-Schiff (PAS) (Figure 2). Furthermore, nonspecific lymphocytic thyroiditis was seen around the nodule.

On immunohistochemical analysis, cells that form the nodules stained positive for thyroglobulin antibody; there was no staining for chromogranin, calcitonin, carcinoembryonic antigen (CEA), and cytokeratin (CK) 19. Hector Battifora Mesothelial 1 (HBME-1) was found to be focal weak positive.

No complications occurred after the surgery. The patient was discharged on the first postoperative day. L-Thyroxine treatment was initiated. Control examination on cervical US was performed 1-year postoperation. No residual tissue or metastatic lesions were detected. A written informed consent was received from the patient.

DISCUSSION

According to World Health Organization's (WHO) classification of Endocrine Organ Tumors, HTT is described as "an uncommon tumor of follicular origin characterized by trabecular pattern of growth and marked intra-trabecular hyalinization (3). HTT is a well-circumscribed, encapsulated lesion and usually asymptomatic; it can be seen in forms of single or numerous nodules or incidentally after thyroidectomy. Mostly it is common in middle-aged women; female:male ratio is 6:1. Rarely, HTTs are associated with chronic lymphocytic thyroiditis or Hashimoto's thyroiditis (4).

The basic histological structure of HTT is characterized with a hyalinizing trabecular pattern, cytoplasmic inclusions at cell cytoplasm and matrix, and nucleus with grooves (5). These tumors have the same macroscopic appearance as the classical thyroid adenomas. Their special features are perivascular hyalinization, dominant stroma, and trabecular arrangement. Organoid strictures are similar to papillary carcinoma (5, 6).

Another controversial point on HTT is the benign or malignant status of the tumor. In 1987, when Carney et al. (1) first described the tumor, they said that HTT is a benign lesion and does not cause to vascular invasion or metastasis. After that, HTT was claimed to be a benign lesion in many cases; however, the literature shows malignant forms that cause capsule and vessel invasion or lung and lymph node metastasis (5). In our case, the tumor was well-circumscribed and had no invasion to vessels and surrounding thyroid tissue.

Macroscopically, these tumors are well-circumscribed and encapsulated like other adenomas. Their most distinctive microscopic features are hyalinized stroma-like amyloid and trabecular pattern of tumor cells (1). Due to the organoid structures accompanying this trabecular pattern, they are called "paraganglioma-like adenoma".

Histologically, the detection of intranuclear groove, pseudoinclusions, and psammoma bodies cause confusion with PTC (7). Further, the fact that HTT is accompanied by papillary carcinoma and that they have the same immunophenotypic properties cause interpretations that both tumors are similar, and moreover, that HTT is a special variant of papillary carcinomas. In our case, FNAB raised a suspicion of PTC; however, pathological study of the material showed no PTC near HTT.

Hyalinizing trabecular tumor can be confused with encapsulated variant of medullary thyroid carcinoma. The base of this confusion is the presence of spindle cells and intratrabecular hyalinization that looks like stromal amyloid (8). These tumors can be distinguished from medullary carcinoma as they are negative for Congo red stain, positive for thyroglobulin, and negative for calcitonin(8). In our case, immunohistochemical analysis was negative for calcitonin.

Hector Battifora Mesothelial 1 is a monoclonal antibody found in mice that is used as a marker for malignant mesothelioma cells. Its sensitivity is 80%-90% and specificity is between 60% and 96% for cancers originating from follicular cells. Mostly it is negative for medullar and undifferentiated carcinoma (9). In our case, immunohistochemical analysis for HBME-1 was focal weak positive.

CONCLUSION

Because of biological and clinical behavior, HTT should be approached as a benign neoplasm; however, although low, its malignant potentiall should not be overlooked (5, 10). It is mostly confused with PTC, but in differential diagnosis, medullary thyroid carcinoma, paraganglioma, and follicular adenoma should be taken into consideration as well.

Treatment of HTT is conservative like PTC, and surgery is performed under similar terms as those for PTC. In the postop-

erative period, HTT should be follow up like a malignant neoplasm (10). Wider case studies with suitable follow-ups will be helpful in explaining HTT development and behavior.

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

Peer-review: Externally peer-reviewed.

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

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 152-154
DOI: 10.5152/turkjsurg.2017.3279

Case Report

Coexistence of gastric multiple neuroendocrine tumors with unusual morphological features and gastric signet-ring cell carcinoma

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ABSTRACT

The coexistence of signet-ring cell carcinoma and neuroendocrine tumors is very rare. We report a 57-year-old man who presented with a history of weight loss and nausea. Gastric mucosal biopsies obtained during gastrointestinal endoscopy revealed a gastric signet-ring cell carcinoma. The patient underwent a total gastrectomy with a standard D2 lymph node dissection. Ten individual tumors were detected in the resected specimen. Based on the histopathological and immunohistochemical findings, the final diagnosis was co-existing signet-ring cell carcinoma and neuroendocrine tumor. Spindle-shaped cells and extracytoplasmic mucin were noted in some tumor cells forming the neuroendocrine component. This case is a rare synchronous tumor because of its unusual neuroendocrine component.

Keywords: Synchronous, gastric, mucin-producing, spindle, neuroendocrine tumor

INTRODUCTION

The coexistence of signet-ring cell carcinoma (SRCC) and neuroendocrine tumor (NET) is very rare (1). SRCC is a histological type in which more than 50% of the isolated tumor cells contain intracellular mucin (2). Gastric NETs originate from the neuroendocrine cells that are dispersed throughout the stomach, and constitute a very heterogeneous group clinically and pathologically. There is scant literature on synchronous tumors of the stomach that combine SRCC and NET with the presence of extracytoplasmic mucin and spindle-cell morphology. We report this case and discuss the potential etiologies and pathological features of this rare presentation.

CASE PRESENTATION

A 57-year-old man with a history of chronic atrophic gastritis with complete intestinal metaplasia and hypertension presented with a 2-month history of weight loss and nausea. His physical examination and laboratory results were within normal limits. Upper gastrointestinal endoscopy showed mucosal ulceration and edema in the corpus. Multiple mucosal biopsies revealed gastric SRCC histologically. Computed tomography of the abdomen showed circular thickening of the corpus wall. The patient underwent a total gastrectomy with a standard D2 lymph node dissection. The resected specimen contained 10 different tumors. One was a centrally deep ulcerated mass (1.2×0.7×0.5 cm) and the other nine were exophytic, tan-colored polypoid masses (diameter of the largest polyp was 1.1×1.1 cm) that were similar in appearance to a submucosal tumor at the corpus of the stomach. Pathologically, the ulcerated mass was a gastric SRCC that arose from the gastric mucosa and invaded the submucosa (Figure 1). The tumor cells of the SRCC were positive for pancytokeratin, epithelial membrane antigen, and Ki67 (70% of labeled cells). Histopathologically, the other nine polypoid tumors demonstrated polygonal, round, spindle-shaped features with vesicular nuclei cells arranged in trabecular, nested, and plexiform patterns in the submucosa and muscular layer, suggesting neuroendocrine cell proliferation (Figure 2). No necrosis or mitosis was observed. The tumor cells of the polypoid tumors were positive for pancytokeratin, synaptophysin, chromogranin A, CD57, protein gene protein 9.5 (PGP9.5), and Ki67 (2% of labeled cells) (Figure 3).

Immunostaining for mucins indicated that the NET cells expressed MUC5AC and MUC1. These cells were negative for gastrin, serotonin, p53, CD34, CD117, and vimentin. To investigate the presence of neuroendocrine differentiation of SRCC tumor cells, an immunohistochemical study was performed. The signet-ring cells were negative for synaptophysin, chromogranin A, and CD57 (PGP9.5). Spindle-shaped cells and extracytoplasmic mucin were noted in some tumor cells of the neuroendocrine component. Mucicarmine staining of the neuroendocrine cells with a different morphology showed luminal positivity; in contrast, the cytoplasm of the SRCC tumor cells stained for mucicarmine (Figure 3). There was no transition between SRCC and NET, and the latter contained mucin-producing, spindle-shaped cells. These histopathological and immunohistochemical findings led to a final diagnosis of a collision tumor composed of a SRCC and NET (Grade 1, according to the WHO 2010 criteria) of the stomach. No

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Cite this paper as:
Uğraş N, Sarkut P, Yerci Ö, Öztürk E. Coexistence of gastric multiple neuroendocrine tumors with unusual morphological features and gastric signet-ring cell carcinoma. Turk J Surg 2018; 34: 152-154.

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Received: 09.07.2015
Accepted: 19.08.2015
Available Online Date: 03.01.2018

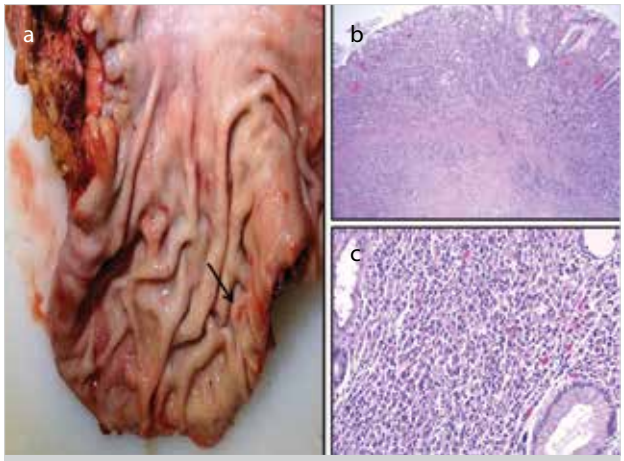

Figure 1. a-c. (a) Grossly, the resected specimen was a tan-red tumor mass with ulceration in the stomach (arrow), (b) Microscopically, the ulcerated mass was signet-ring cell adenocarcinoma (×200, H&E stain), (c) Signet-ring cell carcinoma cells with eccentric nuclei and abundant cytoplasm (×400, H&E stain)

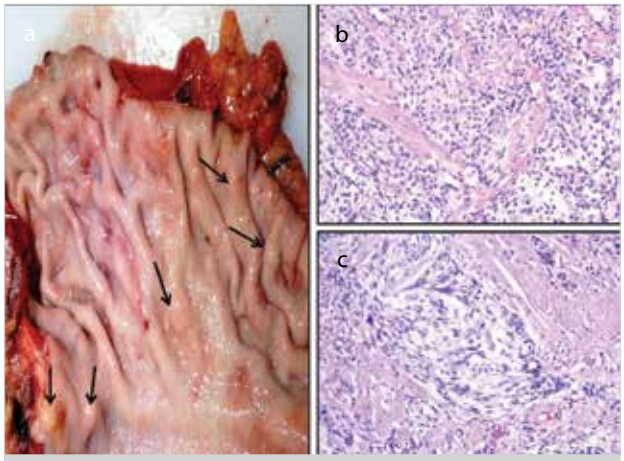

Figure 2. a-c. (a) Grossly, the resected specimen comprised tan-yellow polypoid masses (arrow), (b) Microscopically, the polypoid masses contained uniform populations of small cells with a trabecular, solid growth pattern (×400, H&E stain), (c) Cords of neuroendocrine cells with a spindle shape, mucinous matrix, and a more diffuse area of sheet-like growth

lymphatic permeation, vascular invasion, or perigastric lymph node involvement was observed for either component. The adjacent gastric mucosa showed chronic active gastritis with prominent complete intestinal metaplasia. No *Helicobacter pylori* was detected.

Postoperatively, the patient recovered uneventfully and had no surgical complications. The patient was treated with adjuvant chemotherapy. Follow-up after one year showed no evidence of recurrence or metastasis. A signed written informed consent was taken from the patient.

DISCUSSION

The incidence of gastric NET has increased with the development of imaging modalities and increased awareness. SRCC is an unfavorable subtype of gastric carcinoma that may require more aggressive treatment, and which typically lacks cell cohesion and, therefore, expands in an infiltrative pattern (2).

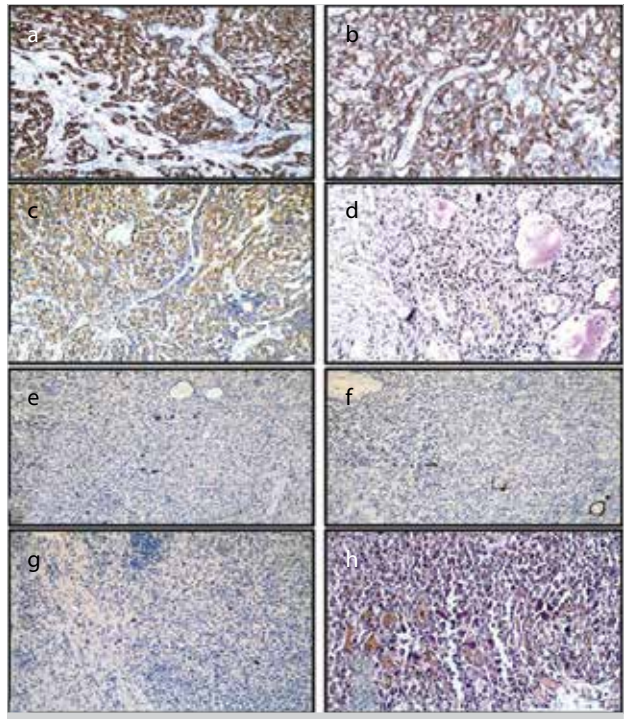

Figure 3. a-h. Immunohistochemical and histochemical findings. (a-c) Neuroendocrine tumor cells expressed PGP9.5, CD57, and synaptophysin, (d) Mucicarmine staining showed focal luminal positivity in the NET component, (e-g) Signet-ring cell carcinoma component cells did not stain for PGP9.5, CD57, or synaptophysin, (h) Mucicarmine staining showed epithelial mucin within the cytoplasmic vacuoles of the signet-ring cells, (a-h) Magnification, ×400

The 2010 World Health Organization (WHO) classification classifies gastric NETs into the following five categories: 1) NET Grade 1, well-differentiated endocrine tumor; 2) NET Grade 2; 3) neuroendocrine carcinoma; 4) mixed adenoneuroendocrine carcinoma; and 5) hyperplastic and preneoplastic lesions (3). NET G1 tumors are composed of small-to-medium-sized round-to-polygonal cells with scant-to-moderate amounts of eosinophilic cytoplasm with an organoid, trabecular pattern (3). In this case, all of the NETs were evaluated as Grade 1 according to the WHO 2010 criteria. Various morphological features similar to those presented here can be observed in NETs, such as spindle-shaped cells, acinar cells, signet-ring cells, and mucin-producing cells (goblet cells) (4, 5). The presence of mucin in the neuroendocrine component is reminiscent of goblet cell carcinoid. Goblet cell carcinoid is a special type of neuroendocrine tumor that usually occurs in the appendix, but may occasionally be present in other gastrointestinal organs (6). Gui defined the gastric localization of goblet cell NETs (6). Unlike normal NETs, these tumors contain co-existing mucin-laden goblet-shaped cells and neuroendocrine cells arranged in nests or clusters, with weak or partial immunopositivity for neuroendocrine markers (7). The mucin in these tumors tends to be intracytoplasmic (5, 6). In our case, the mucin was extracytoplasmic and there were no goblet cells. The neuroendocrine cells with extracytoplasmic mucin and a spindle cell morphology may be a new cell variant in gastric NETs.

In a recent study, Domori et al. (8) investigated the mucin phenotype in gastric neuroendocrine neoplasms. No cases of NET Grade 1 and Grade 2 expressed the mucin markers MUC5AC,

MUC6, or MUC2. Conversely, neuroendocrine carcinoma cases had higher rates of positivity for each mucin marker. In contrast, in our case, the NET Grade 1 tumor cells expressed MUC5AC and MUC2.

Synchronous tumors are believed to result from two separate neoplasms at the primary or another site and may behave differently. The tumor histopathological and immunophenotypic features may be discrete or the same with clear demarcation of the two tumors, indicating that this lesion is a synchronous tumor consisting of SRCC and NET morphologically, consistent with mucin-producing cells. Few cases of gastric NETs coexisting with adenocarcinoma have been reported, and only two have involved SRCC (1).

These findings suggest that chromosomal analysis using comparative genomic hybridization could reveal whether the neuroendocrine component is related to SRCC clonally or whether they are in fact unrelated tumors.

CONCLUSION

This case was a rare example of synchronous tumors because its neuroendocrine component tumor cells contained extracytoplasmic mucin and were spindle-shaped; these attributes are not seen in classic gastric NET Grade 1 tumors.

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

Author Contributions: Concept - N.U., Ö.Y.; Design - N.U., Ö.Y.; Supervision - Ö.Y., E.Ö.; Funding - E.Ö.; Materials - N.U., P.S., E.Ö.; Data Collection and/or Processing - N.U., P.S., Ö.Y., E.Ö.; Analysis and/or Interpretation - N.U., Ö.Y., P.S.; Literature Review - N.U., P.S., Ö.Y.; Writer - N.U., Ö.Y.; Critical Review - Ö.Y., E.Ö.; Other - N.U.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 155-157
DOI: 10.5152/turkjsurg.2017.3211

Case Report

Laparoscopic surgical transmesocolic jejunostomy: A new surgical approach

Alberto Pagan, Alessandro Bianchi, José Antonio Martínez, Marina Jiménez, Francisco Javier Gonzalez

ABSTRACT

In cancer patients with tumors of the upper gastrointestinal tract, dysphagia and cachexia require gastrostomy or jejunostomy as the only options for enteral access for long-term feeding. In this article, the authors describe a modified placement of laparoscopic feeding jejunostomy applied during laparoscopic oncology layering technique. After performing an exploratory laparoscopy, a feeding jejunostomy is performed using a Foley silicon catheter, through an eyelet in the mesentery of the descending colon. After completing the introduction of the jejunal probe according to the Witzel technique, the intestinal segment of jejunum is attached to the internal sheath of the mesocolon using sutures polysorb 2/0, with the aim of removing the possible internal hernia and a jejunal torque that could cause an intestinal obstruction. There were no intraoperative complications or mortality. The technique described here provides most of the benefits of laparoscopic jejunostomy feeding, avoiding the possible internal hernia.

Keywords: Jejunostomy, enteral nutrition, upper gastrointestinal tumors

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Cite this paper as:
Pagan A, Bianchi A, Martínez JA, Jiménez M, Gonzalez XF. Laparoscopic surgical transmesocolic jejunostomy: a new surgical approach. Turk J Surg 2018; 34: 155-157.

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Received: 26.05.2015
Accepted: 29.08.2015
Available Online Date: 03.01.2018

INTRODUCTION

Nutrition in patients with cancer of the upper gastrointestinal tract is essential for a good quality of life. Often patients suffering from this type of cancer are malnourished or cachectic at the time of diagnosis. In these patients, feeding plays a crucial role, even as part of a palliative treatment. Several studies have shown the benefits of enteral feeding over parenteral feeding. Depending on the location of the tumor and the clinical stage, there are several options available for the administration of enteral feeding. Since the introduction of percutaneous endoscopic gastrostomy and gastrostomy placed under radiographic control, surgical techniques such as gastrostomy or jejunostomy have fewer indications. However, when the new techniques described above cannot be performed, surgery is again useful and essential. Most surgical techniques are used in patients with tumors of the upper gastrointestinal tract, head, and neck where the noninvasive techniques are impossible or dangerous to perform. In these patients, open gastrostomy and jejunostomy are the only option for enteral access. Since the first report of laparoscopic jejunostomy described by O'Regan in 1990, there have been several technical publications of laparoscopic feeding jejunostomy. The existence of multiple procedures indicates that there is no standard procedure (1).

CASE PRESENTATIONS

Clinical Cases

Case 1: A 58-year-old male patient with an adenocarcinoma of the gastric antrum presented food intolerance and weight loss of nearly 15 kg in 2 months. In the extension study, the gastroscopy reported the presence of abundant food remains and proliferative and ulcerated lesion in antral region that did not allow the passage of an endoscopic tube. The biopsy of the ulcerated lesion was positive for intestinal type adenocarcinoma. Computed tomography scan showed lymphadenopathy in the left cardial region and lesser gastric curvature of 12 mm and objectified gastric wall thickening with signs of externalization. Exploratory laparoscopy was indicated. Peritoneal lavage was negative for tumor cells. Because of this, a feeding jejunostomy was placed.

Case 2: A 62-year-old female patient was diagnosed with gastric linitis and weight loss of 17 kg in 5 months. Gastroscopy showed submucosal infiltration from the cardia to the antrum. Endoscopic biopsies were negative. The echo-endoscopy showed a submucosal thickening of approximately 1 cm. Due to severe dysphagia and cachexia, laparoscopic jejunostomy placement for enteral feeding was performed.

Preoperative period: Informed consent was obtained in accordance with local regulations for both patients. Standard perioperative antibiotic prophylaxis was carried out with 2 g of amoxicillin clavulanic Ev 30 min before surgery. Antithrombotic prophylaxis was applied including mechanical and pharmacological prophylaxis with low molecular weight heparin LMWH (40 mg of enoxaparin sodium).

Position of patient: The procedure was performed under general anesthesia. The patient was placed in prone position with arms outstretched to the sides. The operator was placed between the patient's legs, the first assistant on the patient's right side and the scrub nurse on the left side of the patient.

Trocar placement: Two 11-mm trocars and a 5-mm trocar were used. Pneumoperitoneum was performed through a Verres needle inserted in left hypochondrium. A pneumoperitoneum of 12 mmHg of CO2 was achieved. The first trocar was placed in the middle left clavicular line. The remaining trocars were placed depending on the anatomical characteristics of the patient.

Surgical Technique

Exploratory laparoscopy was performed using an optical 30° camera. For the inspection of the abdominal cavity, for assessing the size of the tumor and its spread, and the possible presence of metastases were used standard tools were used.Peritoneal lavage is performed to rule out the peritoneal spread of tumor cells. Samples are taken for pathologic examination and to detect HER2 receptors.

A loop of jejunum was selected at a distance of 20 cm from the Treitz ligament. The descending colon was set to be free from the left parietocolic wall and a little hole was made in the left mesenteric leaf. A small incision was made in the abdominal wall, in correspondence to the anterior axillary line.In the planned point, jejunum was opened and a Foley catheter was introduced and placed in accordance with Witzel technique. The permeability of the catheter balloon was checked and filled with 2 ml of distilled water. Jejunal segment was fixed to the mesenteric sheet of the descending colon.

Results

There were no intraoperative complications. Mean operative time was approximately 45 min. There was no blood loss. The short-term outcome was good. There were no postoperative complications or mortality. The use of the jejunostomy was initiated within the first 24 postoperative hours. Then patients were transferred to the oncology unit where underwent the neoadjuvant treatment. The results of the peritoneal fluid tests showed no cancer cells in both patients. Based on the intraoperative findings, the first patient received a neoadjuvant treatment and then a laparoscopic subtotal gastrectomy was performed. The second patient was treated by palliative treatment.

DISCUSSION

Malnutrition and cachexia are often symptoms of tumors of the upper gastrointestinal tract. In unresectable or resectable carcinomas of the head and neck, surgery and radiochemotherapy are routinely performed; therefore, the use of enteral prophylactic approach, as jejunostomy, allows improving the quality of life of patients and prevents the complications of malnutrition during treatment. The progress of noninvasive techniques has shifted the surgical approach. In rare cases, when there is an obstruction of the oropharyngeal and esophageal region, the use of surgical techniques is required to place a jejunostomy catheter or to perform gastrostomy. The procedures performed at present are Witzel jejunostomy, needle catheter jejunostomy, jejunostomy through a serous tunnel, and jejunostomy in Roux-Y. The multiplicity of procedures, essentially reflect the need to find an optimal method as the literature describes (1).

Despite the advantages of feeding by a jejunostomy, serious complications, such as internal hernia and intestinal volvulus, have been described-complications that can be life threatening. Because of this, jejunostomy placement has been questioned by some authors (2); however, other authors (3), knowing its complications, systematically placed the jejunostomy tube during upper gastrointestinal surgery for postoperative enteral nutrition. The frequency of major surgical complications varies from 2.1% to 3.6%. One of this is the intestinal obstruction due to a volvulus around the jejunostomy tube site. In a large study, intestinal obstruction and volvulus occurred in 0.14% patients (4).

The aim of this study was to describe a surgical technique for the jejunostomy placement during laparoscopic staging of two consecutive patients with advanced cancer of the upper gastrointestinal tract. The technique presents the same benefits of the laparoscopic approach, as an early reintroduction of the enteral diet. Furthermore, this technique does not limit a second surgery, such as a total gastrectomy, especially in the use of the afferent loop, and reduces a possible serious complication related to the formation of an internal hernia.

The main drawback of this method is due to the lateralization of the jejunostomy tube that could limit patient autonomy. According to us, the tunneling of the jejunostomy catheter to the anterior abdominal wall would minimize this effect.

CONCLUSION

This new laparoscopic transmesocolic approach is as feasible as other minimally invasive techniques and can be used during a staging surgery and when a need for nutritional support is required. Transmesocolic approach permits the prevention of internal hernia and intestinal volvulus, the two main complications related to the placement of a jejunostomy. Our proposal is to perform an anchorage of the jejunum to peritoneal sheet of the descending mesocolon that involves the parietal fixing of the probe of the jejunostomy. Further studies in larger groups of patients are needed to evaluate the long-term results of this procedure.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.P.; Design - A.P., A.B.; Supervision - X.F.G.; Resource - A.P., A.B.; Materials - A.B.; Data Collection and/or Processing - A.B., M.J.; Analysis and/or Interpretation - A.P., A.B.; Literature Search - A.B., J.A.M., M.J.; Writing Manuscript - A.P., A.B.; Critical Reviews - X.F.G.

Acknowledgements: The technical assistance of the nurse staff of the General Surgery Department is gratefully acknowledged.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 158-161
DOI: 10.5152/turkjsurg.2017.3205

Case Report

Chronic visceral ischemia: An unusual cause of abdominal pain

Turan Acar[1], Volkan Çakır[2], Nihan Acar[1], Kemal Atahan[1], Mehmet Hacıyanlı[1]

ABSTRACT

Chronic visceral ischemia is described as postprandial abdominal pain caused by intestinal hypoperfusion. Chronic visceral ischemia arising from the stenosis of major mesenteric arteries can cause death. Chronic abdominal pain, weight loss, and sitophobia are the major symptoms. The main cause of chronic visceral ischemia is atherosclerosis; Doppler ultrasonography, tomographic angiography, and magnetic resonance angiography can be used for diagnosis. The gold standard method is mesenteric catheterized angiography. Surgical bypass or endovascular balloon angioplasty and stent replacement can also be performed to prevent serious complications and death. A total of three patients, two male and one female, applied to emergency services with blunt abdominal pain lasting a few hours that started after meals and was located in the epigastric and periumblical regions. The patients were diagnosed with chronic visceral ischemia after screening tests and physical examination. Mesenteric catheterized angiography was performed immediately in all the cases. Balloon angioplasty and stent replacement were performed on the stenoses, and occlusions were detected. Mesenteric catheterized angiography may be preferred in cases with strong clinical suspicion; balloon angioplasty and stent replacement can also be used as treatments with lower rates of complications.

Keywords: Chronic mesenteric ischemia, superior mesenteric arteries, balloon angioplasty, stent

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Cite this paper as:
Acar T, Çakır V, Acar N, Atahan K, Hacıyanlı M. Chronic visceral ischemia: An unusual cause of abdominal pain. Turk J Surg 2018; 34: 158-161.

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This study was presented at the 19th National Surgical Congress, 16-20 April 2014, Antalya, Turkey.

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Received: 17.05.2015
Accepted: 30.08.2015
Available Online Date: 03.01.2018

INTRODUCTION

Chronic mesenteric ischemia (CMI) is described as postprandial abdominal pain caused by intestinal hypoperfusion. CMI is a rare condition that is caused by stenosis of the major mesenteric arteries and can be fatal; it was first described by Goodman as "abdominal angina" in 1918. CMI has a mostly multifactorial etiology; it is the most common cause of atherosclerosis in the celiac artery (CA), superior mesenteric artery (SMA), and inferior mesenteric artery (IMA) (1). CMI arising from stenosis of the major mesenteric arteries can cause death. However, arterial dissection can occur due to vasculitis, fibromuscular dysplasia, radiation, and use of cocaine. General risk factors are smoking, hypertension, diabetes mellitus (DM), and hypercholesterolemia.

The clinical course progresses slowly and is difficult to diagnose. The major symptoms are 15 to 60 minutes of abdominal pain starting 1 to 4 hours after eating and weight loss. Most patients are over 60 years of age, and CMI is seen three times more often in women than in men. In a study, patients over 65 years of age were found to represent 17.5% of cases with more than 70% obstruction of the mesenteric arteries (2). Chronic mesenteric ischemia can cause intestinal infarction and death if not treated. The main cause of CMI is atherosclerosis; Doppler ultrasonography (US), tomographic angiography (CTA), and magnetic resonance angiography (MRA) can be used for diagnosis. The gold standard method for accurate diagnosis is mesenteric catheterized angiography (3). The first successful open surgical procedure for CMI was performed by Shaw in 1985. Since then, surgical repair has been used as a standard treatment for CMI. However, endovascular revascularization (ER) is currently becoming more popular because ER is minimally invasive and also has lower rates of morbidity and mortality than angioplasty and stent of the mesenteric artery (4). Herein, we report three cases of CMI who presented with abdominal pain and our approach to treatment.

CASE PRESENTATION

The clinical and morphological data of the patients are summarized in Table 1. A total of three patients, two male and one female, applied to emergency services with blunt abdominal pain that started after meals, lasted a few hours, and was located in the epigastric and periumblical regions. The mean age of the patients was 50.3. The male patients had a history of smoking of one pack a day, DM, hypertension, coronary artery disease, and chronic obstructive lung disease. The female patient did not smoke and did not have a history of any other medical conditions. The patients' vital signs were stable.

In physical examination, the abdominal quadrants were sensitive to palpation, while no defense or rebound was observed. Only elevated D-dimer and fibrinogen levels were obtained in laboratory tests. All

Table 1. Clinical and morphological findings of the patients

	Patient 1	Patient 2	Patient 3
Sex	Male	Male	Female
Age	57	45	49
Comorbidity	CAD, DM, HT, COPD, CVE	CAD, DM, HT	-
Pathology	SMA occlusion	SMA occlusion	SMA occlusion
Treatment	Balloon angioplasty and stenting	Balloon angioplasty and stenting	Balloon angioplasty and stenting
Postoperative treatment	Clopidogrel 75 mg+ASA 100 mg	Clopidogrel 75 mg+ASA 100 mg	Clopidogrel 75 mg+ASA 100 mg
Postoperative complication	Portal vein thrombosis and pancreatitis	-	-
Hospitalization time (days)	14	10	7
Follow-up time (months)	12	12	4
Mortality	-	-	-

CAD: coronary artery disease; DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; CVE: cerebrovascular events; ASA: acetylsalicylic acid

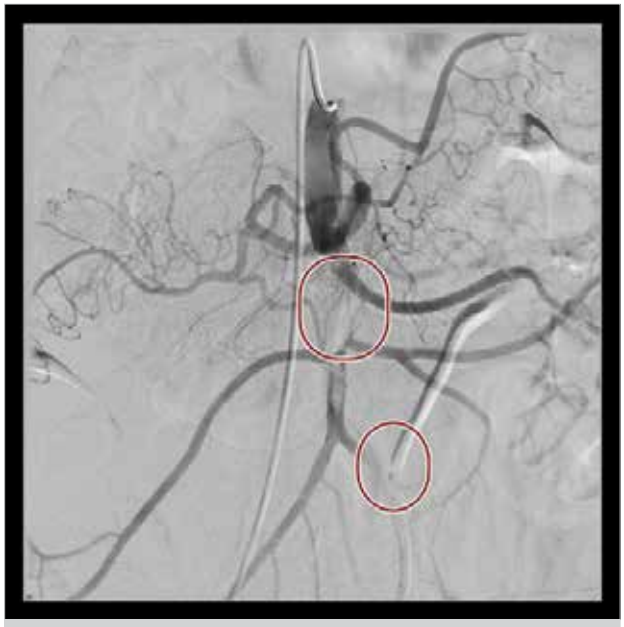

Figure 1. Angiography showing SMA and sigmoidal artery occlusion (marked with circle)

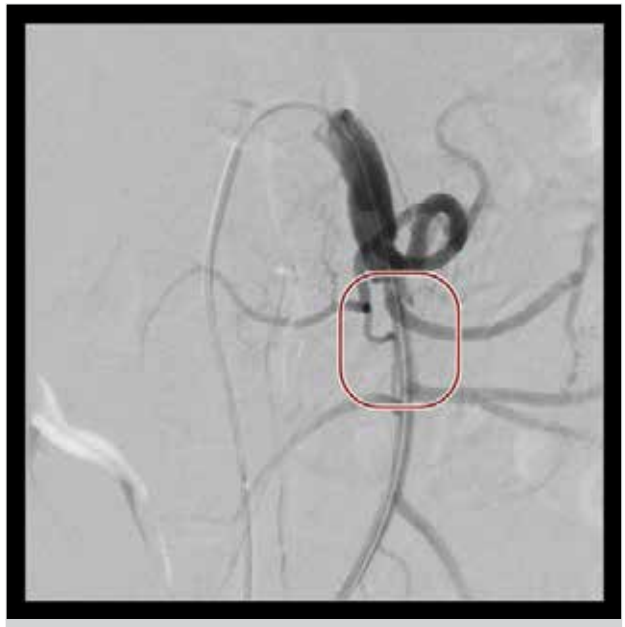

Figure 2. A 5 mm stent is placed in the SMA with the guidance of a wire (marked with circle)

patients were investigated with abdominal contrast-enhanced computerized tomography, revealing a thrombus in the SMA. The patients were diagnosed with CMI after screening tests and physical examination. The patients were diagnosed with CMI due to the obliteration of the splanchnic artery, and revascularization of SMA was planned for treatment. ER, which is a minimally invasive method, was chosen due to its lower morbidity and mortality rates. Mesenteric catheterized angiography was performed immediately in all the cases. Mesenteric catheterized angiography was performed under local anesthesia in our Department of Interventional Radiology. Two of the cases had occlusions in the SMA, while the third patient had two different obstructions in the SMA and sigmoidal artery (Figure 1). Balloon angioplasty (PTA) and a 5 mm stent replacement was performed for each occlusion (Figure 2), and angiographic images taken after the procedure showed no obliteration (Figure 3). Balloon angioplasty and stent replacement were performed on each detected stenosis and occlusion.

All patients were heparinized with 500 U before the procedure, and Clopidogrel 75 mg and acetylsalicylic acid (ASA) were given after the procedure. During follow-up, one patient had pancreatitis and thrombosis of the portal vein and was medically treated. The other two cases had no additional complications. All three patients under follow-up remained free of disease. All the patients in this study were informed about the procedures in detail and signed informed consent forms. The necessary consent was obtained from the patients to perform a scientific study.

DISCUSSION

Chronic mesenteric ischemia, or abdominal angina, is characterized by postprandial abdominal pain and weight loss due to the loss of intestinal blood flow secondary to obstructions in two or three splanchnic vessels. CMI, which is commonly caused by atherosclerosis, is one of the less common causes of mesenteric ischemia, with a rate of 5%. Other causes of CMI

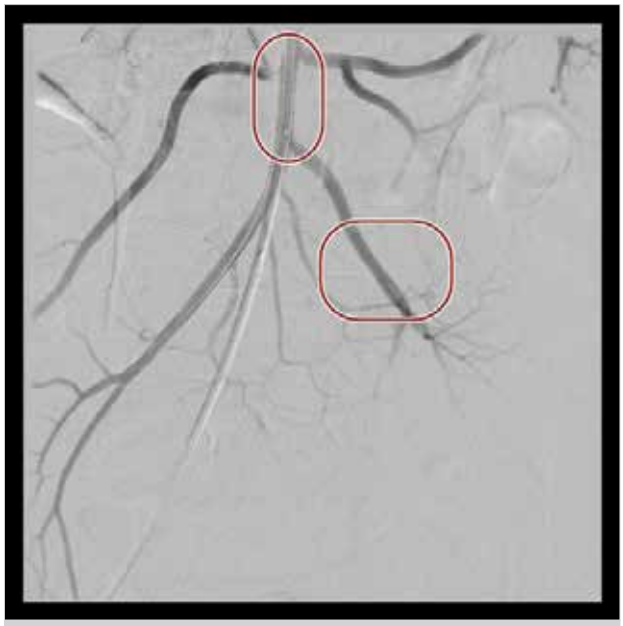

Figure 3. Open flow in the SMA and the sigmoidal artery (marked with circle)

include fibromuscular dysplasia, vasculitis (Takayasu's arteritis, giant cell arteritis, polyarteritis nodosa, systemic lupus erythematosus, and thromboangiitis obliterans), malign tumors, and radiation. The major risk factors are hypertension (57%), cardiovascular disease (51%), renal failure or nephropathy (30%), and diabetes (25%). Two of our patients had comorbid diseases of hypertension, DM, and coronary artery disease; CMI was thought to evolve due to atherosclerosis in these cases. The mean age of CMI patients is reported as 68, and the incidence is similar between male and female patients (5).

The blood flow in the intestines is approximately 25% in hunger; however, after meals, the blood flow increases to 35%. This explains why the symptoms of CMI intensify after eating. In chronic ischemia, because of the well-developed collateral circulation, symptoms usually arise only if at least two major arteries (CA, SMA, and IMA) are obstructed. Most cases remain asymptomatic, although they show more than 50% occlusion. Chronic mesenteric ischemia results in acute ischemia and bowel infarction in 26%-66% of untreated cases (6). Mesenteric ischemia develops in 6% of asymptomatic cases with serious mesenteric obstruction during a mean follow-up of 2.6 years.

Because of the gastrointestinal symptoms, mesenteric ischemia, and the mortality rate of 86% in these cases, CMI patients should be closely followed up even if they are asymptomatic. Anamnesis and physical examination are important factors in the diagnosis of CMI. Colored Doppler ultrasonography, MRA, and computerized tomographic angiography can be used as additional diagnostic techniques. A noncontrast CT examination to assess the presence of vascular calcifications should always be included. CT may also demonstrate nonvascular causes of abdominal pain, such as inflammatory disease or neoplasm. Furthermore, there may be findings that help differentiate between an acute and a chronic process; bowel wall thickening, pneumatosis, and portomesenteric gas indicate an acute process and are absent in CMI. Conventional angiography is the gold standard method for screening the main artery and branches of the mesenteric artery, in addition to stent replacement treatment and balloon angioplasty if stenosis is detected (7).

Treatments intended to address symptoms, especially postprandial abdominal pain, and to prevent bowel infarctions are necessary for symptomatic CMI patients. The initial conservative approach should include smoking cessation, bowel rest, and vasodilatator drugs. Some patients can benefit from nitrates for a short time. In cases where conservative methods fail, revascularization should be the next step. The procedure of thromboendarterectomy of the SMA was first performed by Mikkelsen in 1958. All open surgical procedures, such as transartic endarterectomy, reimplantation directly into the aorta, and antegrade or retrograde bypass, have advantages and disadvantages. The most commonly applied method is prosthetic graft bypass. A high rate of success (90%-100%) of surgical methods in reduction of symptoms has been reported in the literature (8). However, the mortality and morbidity of surgical procedures were stated to be 5%-12% and 5%-30%, respectively (8). In addition to complications such as ileus, bleeding, intravascular coagulation, and lung, kidney, or liver failure, recurrence of the stenosis was detected in 9%-35% of cases.

Endovascular revascularization was first described in 1980 as an alternative to surgery. Balloon angioplasty and, if needed, stent replacement are the major components of this technique. ER, an effective and less invasive method, has become more popular due to its high rates of technical (90%-100%) and clinical success (80%-100%) in addition to the lower risk of complications (9). Additionally, the risk of open wound is lower in ER than in open surgery. Considering all these reasons, ER is currently recommended, especially for high risk patients. We also obtained satisfying results after ER treatment in our cases.

The most suitable lesions for ER are those with short segments (lower than 10 cm) located near the CA or the SMA ostium. The rate of success was found to be 95% in ostial and 78% in nonostial lesions, with acceptable success of angioplasty in short term follow-up. Single vessel angioplasty is recommended in the literature; however, intervention to other vessels may be necessary in case of failure of the first attempt. SMA angioplasty was reported as sufficient in the first step. Many studies state that stent replacement after angioplasty is preferable in ostial lesions; however, it is essential in dissection and recanalization, with a decrease in the risk of recurrence.

The relative contraindications of ER include acute ischemia, bowel necrosis, acute stenosis excluding ligament compression stenosis, and advanced vascular disease affecting the secondary branches. These cases are more suitable for surgical treatment; however, the complications of perforation, bleeding, and hematoma during the procedure and postoperative distal embolization and arterial dissection may be encountered (10).

CONCLUSION

Colored Doppler ultrasonography is a useful diagnostic method for CMI. However, the assessment can be suboptimal due to diffuse abdominal distension. Mesenteric catheterized angiography may be preferred in cases with strong clinical sus-

picion; it can also allow balloon angioplasty and stent replacement as treatments with lower complication rates.

Currently, due to increases in experience and in the technical quality of the equipment used, ER is much more suitable for the diagnosis and treatment of CMI, especially in high risk patients.

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

Peer-review: Externallypeer-reviewed.

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

Acknowledgements: The authors would like to thank Department of General Surgery and Gastroenterology staff for their cooperation.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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Turk J Surg 2018; 34: 162-164
DOI: 10.5152/turkjsurg.2017.3241

Case Report

The patients with Peutz-Jeghers syndrome have a high risk of developing cancer

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ABSTRACT

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by mucocutaneous hyperpigmentation, and intestinal and extraintestinal multiple hamartomatous polyps. Development of gastrointestinal and extragastrointestinal cancer risk is markedly increased in patients with Peutz-Jeghers syndrome. We analyzed five patients from two families diagnosed with Peutz-Jeghers syndrome between 1999 and 2012. This study confirms the actual malignancy potency of PJS. Therefore, we suggest a close follow-up of patients with Peutz-Jeghers syndrome for the risk of malignancy.

Keywords: Peutz-Jeghers syndrome, hamartomatous polyp, intussusception

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder that is characterized by mucocutaneous hyperpigmentation, and intestinal and extraintestinal multiple hamartomatous polyps. It usually occurs in infancy and late adolescence. Although most of the polyps are encountered in the jejunum, they can occur in any other part of digestive system. Development of gastrointestinal and extragastrointestinal cancer risk is markedly increased in patients with PJS (1, 2). We analyzed five patients from two families diagnosed with PJS between 1999 and 2012. There were three male and two female patients, and their ages at the initial diagnosis ranged from 2 to 38 years. At the time of diagnosis, all patients had characteristic mucocutaneous hyperpigmentations and multiple polyps in the digestive system. Gastrointestinal cancer occurred in four of the five patients, three of whom developed colon cancer and one of whom developed small intestinal cancer at 32 years of age. One female patient with colon cancer also developed bilateral breast cancer. Three of these patients died within one month to one year after being diagnosed with colorectal cancer. Thus, we aim to present some new clinical features of PJS that have not previously been described in the literature and to discuss again the relationship between PJS and the development of cancer.

CASE PRESENTATIONS

Case 1: The male patient was born in 1970. He was 32 years old when colon cancer was first diagnosed. His father had been diagnosed with colon cancer at 54 years of age, and he died two years later. The patient had four siblings, two of whom were males at 14 and 22 years of age who do not show any signs or symptoms of PJS. The other two siblings described below, one male and one female, had PJS. The patient had undergone partial jejunectomy due to jejunal intussusception at the age of 17. He was admitted to our hospital in 2004 with subileus complaints and apparent perioral and oral hyperpigmentations on inspection. Detailed analysis revealed small intestinal intussusception at two locations and concomitant rectum cancer. The patient then underwent polyp excision (a total of 13 polyps were excised) and Miles operation in the same session. Histopathological examination of the resected specimen revealed signet ring carcinoma, regional lymph node metastasis (27/28), perinodal infiltration, and 13 hamartomatous pedunculated polyps with small intestinal localization, two of which contained adenocarcinoma. Postoperatively, the patient received chemotherapy; however, he died from progressive cancer metastasis one month after surgery.

Case 2: The female patient was born in 1972. She was 32 years old when the colon cancer was first diagnosed. She was the sister of the abovementioned patient. The patient underwent a left hemicolectomy in 1999 due to obstructive left colon cancer. Several small-sized hamartomatous polyps were detected in the small intestine. Histopathological examination revealed mucinous carcinoma. Polypectomy was performed in 2005 to excise adenomatous polyps localized in the colon. The polypectomy was followed by right and left mastectomy in 2007 and 2010, respectively, due to breast cancer. The patient has been healthy since then and has no medical problems in follow-up examinations.

Case 3: The male patient was born in 1980, and was the third affected sibling in the family above (Cases 1 and 2). He was 32 years old when colon cancer was first diagnosed. He was admitted to our hospital with severe abdominal pain, vomiting, and abdominal distention. On inspection, mucocutaneous hyperpigmentation

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Cite this paper as:
Tavusbay C, Acar T, Kar H, Atahan K, Kamer E. The patients with Peutz-Jeghers syndrome have a high risk of developing cancer. Turk J Surg 2018; 34: 162-164

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This study was presented at the 18th National Surgical Congress, 23-27 May 2012, İzmir, Turkey.

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Received: 11.06.2015
Accepted: 06.09.2015
Available Online Date: 03.01.2018

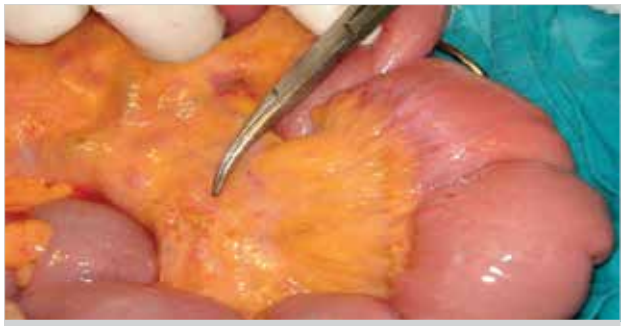

Figure 1. Melanin pigment deposits on mesentery of the small intestine

was detected in the hands, feet, and perioral and oral mucosa. Physical examination revealed a mass on the right side of the umbilicus. A computed tomography scan revealed jejunojejunal intussusceptions. During laparotomy, a small bowel intussusception was detected. Multiple polyps were palpated from the stomach to the colon. Numerous melanin pigment deposits were observed in the mesenteries of both the small intestine and the colon (Figure 1). In addition, a tumoral mass was detected in the duodenum at the level of Treitz. He underwent duodenojejunal resection and side-to-side jejunoduodenostomy. Histopathological examination revealed adenosquamous carcinoma and multiple hamartomatous polyps. This patient was discharged on the 11th day postoperatively and started receiving cancer chemotherapy. However, systemic metastasis was detected one month after the operation, and he died two months later.

Case 4: The male patient was born in 1965. He was 38 years old when colon cancer was first diagnosed. The patient did not display typical PJS symptoms initially. However, he had diffuse vitiligo and hypospadias on inspection. He underwent rectal polyp excision twice in 1985 and 1986 at different healthcare centers, intussusception operation in 1986, and undescended testicle surgery in 1996. PJS was diagnosed in one of his two daughters, but his son, who was 2 years old, did not display any signs or symptoms of the disease. The patient underwent surgery due to multiple colon polyps following his admission on April 30, 2003 due to polyp protrusion from the anus. The patient underwent total colectomy, loop ileostomy, and J-pouch ileoanal anastomosis. Histopathological examination revealed moderately differentiated adenocarcinoma and regional lymph node metastasis accompanied by multiple tubular, villous, and tubulovillous adenomas in the colon. The patient died due to diffuse liver and lung metastases, despite systemic cancer chemotherapy, one year after surgery.

Case 5: The female patient was born in 1993, and she was just 2 years old at the time of diagnosis of PJS. She is the daughter of the abovementioned patient (Case 4). She underwent endoscopic polyp resection several times on detection of large-sized polyps localized throughout the whole gastrointestinal system from the stomach to the colon. In addition, she underwent partial small intestinal resection in 2010 due to jejunal intussusception. The patient is now healthy and under periodic follow-up.

All the patients in this study were informed about the procedures in detail and signed the informed consent form. Necessary consents were obtained from the patients to perform scientific work.

DISCUSSION

Peutz-Jeghers syndrome is an autosomal dominant disorder with familial occurrence of gastrointestinal hamartomatous polyps in association with mucocutaneous hyperpigmentation and occurs in approximately 1 in 8300 to 280,000 live births (1, 2). The cause of PJS is a mutant gene named STK1, also known as LKB1. This gene is localized at 19p34-p36 and is a serine/threonine kinase that controls growth regulation. Aretz et al. (3) studied large STK11 deletions in 56 patients with PJS using the combination of sequence analysis to detect point mutations and multiplex ligation-dependent probe amplification (MLPA). They found that the STK11 mutation detection rate was 94%. Further, other authors reported that mutations could be observed in all patients with PJS (4, 5). We were unable to perform genetic analyses in our patients due to technical and financial reasons. The earliest symptom of PJS is mucocutaneous pigmentations that occur in the first year of life in about 95% of patients. The melanotic pigmented macules are dark brown or bluish brown in color and 1-5 mm in size; these lesions can occur at many sites on the body in children, while in adults, the characteristic buccal lesions are most evident. They can be located on the vermilion border of the lips (94% of patients), buccal mucosa (66%), hands (74%), feet (62%), lips, eyes, nostrils, and perianal area (6). Histological examination of the pigmented macula reveals increased melanin in basal cells. We detected 10 to 30 circle- or ovoid-shaped melanin pigment deposits of 1-3-mm diameter that we named "sprinkled black pepper" in the mesentery of the intestines in one patient with PJS; this symptom has not been reported in the literature to date.

The Peutz-Jeghers polyp is a true hamartoma with unique histopathological characteristics that consist of a branching structure of connective tissue and smooth muscles lined by normal intestinal epithelium. The hamartomatous polyps in the gastrointestinal system can lead to complications, such as bleeding, obstruction, anal protrusion, and intussusception, which have also been observed in our cases, during the first three decades of life. Although polyps are detected throughout the gastrointestinal tract other than the mouth, the jejunum is the most affected intestinal segment. One of the most commonly observed complications of these polyps is intussusception. Gastrointestinal bleeding may accompany PJS and causes anemia. Bleeding might occur on the surface of the polyp, and considerable attention must be paid as malignancy may also cause anemia. Anemia had developed in all our cases.

The fourth patient, who had vitiligo, hypospadias, undescended testicles, and multiple intestinal and colonic polyps, was operated on due to malignant transformation of these polyps. The small intestinal polyps were hamartomatous in nature. This patient's daughter developed all characteristic lesions of PJS. Therefore, we suggest that this disease belongs to a family of hamartomatous polyposis syndromes including PJS, juvenile polyposis, and Cowden syndrome.

The relation between gastrointestinal carcinoma and PJS has been discussed for many years. It is commonly accepted that the incidence of cancers within the gastrointestinal tract as well as in other organs increases in patients with PJS. Perzin et al. (7) described adenoma and *in situ* carcinoma in a PJS patient who developed polyps for the first time in 1982. In 1987, Giardiello et al. (8) reported that 31 patients with PJS in the United States had a

higher frequency of cancer (48%) and confirmed an excessive risk of gastrointestinal malignancy. In addition, they found an excess of malignancies at a number of other sites. It has been well known that breast cancer, ovarian sex cord tumors, cervical cancer, and feminizing Sertoli cell testicular tumors in prepubertal boys can develop in patients with PJS. Although cancer is uncommon before the age of 30, the risk of development of malignancy becomes important in later years. It has been reported that over 90% of patients with PJS are likely to develop at least one malignancy, either gastrointestinal or elsewhere in the body, by the age of 65 years (9). Of all tumors associated with PJS, breast cancer poses the greatest risk, affecting 32%-54% of patients. Giardiello et al. (10) have determined that the relative risk for gynecological and breast cancers in women increased by 20.3% and that for gastrointestinal cancers increased by 50.3%in PJS patients. Spigelman et al. (6) reported that the relative risks of death from gastrointestinal cancer and death from overall cancer in patients with PJS were 13% and 9%, respectively. The age of onset for many PJS-associated cancers was very young, similar to our series. Particularly, we want to emphasize the importance of regular cancer screening in all patients with PJS who have a first-degree family history of cancer. We use and recommend NCCN surveillance guidelines for screening methods and interval time for patients with PJS (9). Many other polyps may also develop in patients with PJS; polyps showing adenomatous changes frequently emerge in the colon and may be confused with familial adenomatous polyposis.

The risk of small bowel cancer development in PJS patients is low (approximately 12% lifetime risk). The most common gastrointestinal malignancies in PJS patients are seen in colon, pancreas, and stomach. Cancer was localized to the colon in three out of four patients in our series, while the other one was localized to the duodenum. Among non-gastrointestinal cancers (breast, ovary, thyroid gland, lung, and endometrium), the most common is breast cancer (greater than 50% lifetime risk). Although gastrointestinal cancer was seen in four out of five patients in our series, extragastrointestinal cancer (bilateral breast cancer) was seen in one patient. In the present study, which included a relatively small number of patients, malignant neoplasms were found in all patients except one. The patient age at the time of diagnosis of cancer was younger than 50 years in all patients. The development of cancer in such young patients is in good accord with previous reports (10-12). Thus, once a patient, even at a young age, is diagnosed with PJS, it should be kept in mind that the patient might already have cancer or that cancer may develop in the near future. Our study reports that malignancy developed in four out of five patients who were members of two different families. Two different types of rapidly growing malignancies with different histopathological features were detected in two male members of the first family and died within one month of diagnosis, despite radical surgery accompanied by adjuvant chemotherapy. Despite colon cancer and subsequent bilateral breast cancer, the third patient (female) in the same family is still alive. In light of the findings that cancer occurred in the third decade of life on average in the two families reported in our study, it might be hypothesized that members of some families with PJS have a greater risk and/or tendency to show malignant transformation. Therefore, we consider that further studies are required for the genetic screening of patients with PJS who have close relatives with a history of cancer. In conclusion, gastrointestinal or extragastrointestinal cancers were found in four out of five patients with PJS, and three of these patients died due to cancer metastasis. Patients with PJS require close follow-up immediately after the time of diagnosis. In order to reduce the rates of mortality and morbidity in patients with PJS, we suggest that patients must be screened periodically with endoscopy.

CONCLUSION

We conclude that PJS is a precancerous syndrome with a marked predisposition for both gastrointestinal and extragastrointestinal cancers. Additional intensive and systemic evaluations may be required in patients with PJS, especially in young patients with symptomatic disease, and they must be closely followed up due to the risk of development of malignancy.

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

Peer-review: Externallypeer-reviewed.

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

Conflict of Interest: The authors have no conflicts of interest to declare.

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

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