ISSN 2564-6850
E-ISSN 2564-7032

TÜRK CERRAHİ DERNEĞİ 1929

TURKISH JOURNAL OF SURGERY

VOL. 33 | ISSUE 2
JUNE 2017

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 2017 / June 2017 • 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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OPEN ACCESS

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TURKISH JOURNAL OF SURGERY

Instructions to Authors

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

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

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

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

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.

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

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

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

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

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

Tables

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

Figures and Figure Legends

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

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

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

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

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

References

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

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

Table 1. Limitations for each manuscript type

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

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

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

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

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

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

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

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

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

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

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

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TURKISH JOURNAL OF SURGERY

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Editorial

Dear colleagues,

We are pleased to be publishing the second issue of this year in time.

We have previously stated that our performance during this publication period is of utmost importance to us. Owing to the success achieved in previous years, our journal has been accepted to the PubMed. We set some goals to further advance this success and be accepted into international indices.

We are very pleased to witness intense interest and support from our distinguished colleagues. We would like to express that we hope that this interest and support will keep growing.

The current issue includes various valuable reviews, clinical and experimental studies along with several case reports of importance. I would like to inform in advance that in the upcoming issues we will be presenting prestigious studies by Turkish scientists living abroad as well as by scientists from other countries.

I would like to wish a successful career and healthy and peaceful days to all our colleagues. Looking forward to meeting in the September issue.

Prof. Mustafa Şahin

Editor in Chief

Turk J Surg 2017; 33: 49-50
DOI: 10.5152/turkjsurg.2017.3866

Invited Review

Good surgeon: A search for meaning

Andrey L. Akopov[1], Dmitri Y. Artioukh[2]

ABSTRACT

The art and philosophy of surgery are not as often discussed as scientific discoveries and technological advances in the modern era of surgery. Although these are difficult to teach and pass on to the next generations of surgeons they are no less important for training good surgeons and maintaining their high standards. The authors of this review and opinion article tried to define what being a good surgeon really means and to look into the subject by analysing the essential conditions for being a good surgeon and the qualities that such a specialist should possess. In addition to a strong theoretic knowledge and practical skills and among the several described professional and personal characteristics, a good surgeon is expected to have common sense. It enables a surgeon to make a sound practical judgment independent of specialized medical knowledge and training. The possible ways of developing and/or enhancing common sense during surgical training and subsequent practice require separate analysis.

Keywords: Common sense, good surgeon, meaning, training

INTRODUCTION

There is more to surgery than can be answered by modern drive for randomised controlled trials and other studies aimed at pursuit of pure science and knowledge. The art and philosophy of surgery tend to be overlooked, as they are more difficult to define, teach and, perhaps, pass on to the next generations of surgeons through a formal training. The issues of humanity, surgical essence and surgeon's qualities, although rarely discussed nowadays, are no less important for training good surgeons and maintaining their high standards (1). Many surgeons, at least at some stage in their careers, try to define what being a good surgeon really means. In that respect, the authors of this article tried on the basis of selected literature review and personal experience to look into the issue by analysing 1) the important conditions of being a good surgeon and 2) the qualities such a specialist should possess.

CONSEQUENCES FOR TRAINING AND PRACTICE

Characteristics of a good surgeon are inevitably subjective in nature and may have different meanings depending on if the term is being used by professional colleagues, patients and their relatives, or social media. Even an Internet search does not provide an immediate answer to the phrase "good surgeon". The first two hits to come up are related to the qualities of a surgeon and advice on how to become one (2, 3).

Undoubtedly, being a good surgeon is influenced by his or (more and more frequently) her education and training. The education and training should fulfil two main objectives. The first one is to develop good manual dexterity. After all, the crucial part of a surgeon's work is manual. Regardless of how other elements may seem important, a surgeon without adequate manual skills is not a surgeon. The second objective is to acquire a wide range of clinical and scientific knowledge relevant to the chosen specialty. In real life, one often comes across with surgeons who have succeeded in one of these directions but, sadly, not in both. Brilliant technicians can be to some extent lacking in their theoretical and scientific aspects. On the other hand, the desire to obtain extensive theoretical knowledge on complex medical issues often co-exists with a sub-standard progress in the operating room. The readers can judge for themselves whom of the above two categories they would choose to be their surgeon.

Secondly, several features of personality appear to be no less important. Not every trainee who developed high technical skills and acquired sound theoretical knowledge becomes a truly good surgeon. In this context, the authors refer to physical and psychological traits of resilience, ability to work long hours and often in critical situations, improvise if required, and handle difficult situations with calmness and persistence, readiness for the emotional discomfort and even psychological trauma due to adverse and unexpected outcomes of treatment. High intellectual potential, good communication skills, courage and honesty are of paramount importance. A good surgeon should be a leader who is able to accurately

Cite this paper as:
Akopov AL, Artioukh DY. Good surgeon: A search for meaning. Turk J Surg 2017; 33(2): 49-50

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Received: 12.03.2017
Accepted: 12.04.2017

Available online at
www.turkjsurg.com

assess strengths (and weaknesses) of other members of the team ultimately to the benefit of patient care. Participation in scientific research with regular publications is one of the ways of self-improvement and of keeping up-to-date. A good surgeon should be capable of constant and critical analysis of his or her own performance and outcomes objectively comparing them with those of peers. In this respect, it is worth mentioning the views linking the professional success to a practical-minded obsession with the possibility and consequences of failure, and ability to routinely evaluate mistakes (4).

Many similar thoughts have been commented upon in medical books, memoirs of retired surgeons, educational papers and event talks to media correspondents. For example, Johnson of Demand Media divided qualities of a surgeon into mental, social, emotional and psychological, mechanical, educational and even constitutional (3). Apparently the USA Bureau of Labor Statistics warns that would-be surgeons need to have the right constitution and stamina because the requirements of patient care might also call on doctors to lift or turn patients. Does a good lifter make a good surgeon? Interestingly, mechanical hand dexterity was only the fourth in the order of the list of the desired qualities. Despite the defined professional, intellectual and moral goals very few professionals reach the status of a good surgeon in the broad meaning of this phrase. What is the right balance between highly specialised technical skills and wide medical knowledge? Should a surgeon follow his/her trusted clinical experience or engage in the never-ending search for new approaches to treatment? Should he (or she) thrive to artistic and elegant performance in the operating room or practice with maximal technical precision and reliability? Is research experience really that important for a practicing surgeon? Is it truly necessary to spend time improving theoretical and practical knowledge in the chosen surgical specialty or is it better to devote time to enhancing the general knowledge on other medical and even non-medical disciplines? Are kindness and compassion, willingness to help a patient at all cost more valuable than ability to firmly decline unacceptably high-risk interventions? Should a surgeon engage in a lengthy laparoscopic procedure aiming at better cosmetic outcome or employ an open approach and accomplish the operation in a safely and timely manner?

Since there are no simple answers to the above questions, which surgeons face daily, often the only practical way to find the right solution in a tricky situation is to exercise common sense. Common sense can be defined as a sound and prudent judgment based on a simple perception of the situation or facts (5). It is common sense that determines the optimal combination of various, sometimes completely opposite, qualities of an individual surgeon. For a surgeon who is already in possession of the most of the previously described desired qualities the presence of common sense and the ability to exercise it logically is the single most important condition for becoming a good surgeon.

Common sense cannot be formally taught at school or university as it is formed on the basis of native intelligence. Such a discipline cannot be included into curriculums of post-graduate training and examinations. This is a quality moulding at the earlier stage of an individual's development and although it can be enhanced or suppressed during the rest of life, one either does or does not possess this ability. Common sense becomes a link between theoretical knowledge and its practical application in a successful manner. This is what allows some surgeons to perform accurate interpretation of a patient's history, symptoms, signs and results of investigations and establish the correct diagnosis and logical treatment plan. Others who lack common sense are simply less capable of doing it. This is what enables some surgeons to operate relying constantly on their visual and tactile sensations, delicately dissecting tissues in the correct anatomical plane, while others with the same skill cannot perform the task. This is what allows surgeons to make often the most difficult decision on when not to operate. As a rule, only those who possess common sense become successful and good surgeons.

CONCLUSION

In addition to strong theoretical knowledge and practical skills and among many other described qualities that a good surgeon is expected to possess, the presence of common sense is of paramount importance. It enables a surgeon to make sound practical judgments independent of specialized medical knowledge and training. The possible ways of developing and/or enhancing common sense during surgical training and subsequent practice require separate analysis.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.L.A., D.Y.A.; Design - A.L.A., D.Y.A.; Supervision - A.L.A., D.Y.A.; Literature Search - A.L.A., D.Y.A.; Writing Manuscript - D.Y.A.; Critical Reviews - A.L.A., D.Y.A.

Acknowledgements: D.Y.A. is grateful to his surgical trainee, Miss Andrea R. Sheel, whose participation in the discussions about the qualities of a good surgeon helped to shape this article.

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

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

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Turk J Surg 2017; 33: 51-57
DOI: 10.5152/turkjsurg.2017.3870

Invited Review

Lymphedema: From diagnosis to treatment

Oğuz Kayıran[1,2], Carolyn De La Cruz[3], Kaori Tane[1], Atilla Soran[1]

ABSTRACT

Lymphedema is a chronic and progressive disorder resulting from impaired lymphatic system function. In developed countries, upper extremity lymphedema is mainly the consequence of breast cancer surgery in which axillary lymph node dissection and radiation alter upper extremity lymphatic flow.

Diagnosis of lymphedema is made clinically. Nevertheless, there are numerous diagnostic tools available for disease staging. Recently, a new technology namely magnetic resonance lymphangiography has emerged in the medical field to assist in both diagnosis and management.

There are non-surgical and surgical treatment options available. Non-surgical methods are always the first-line treatment; however, surgical options can be explored in appropriate patients. Recent studies focus on the prevention of lymphedema using surgical techniques utilizing axillary reverse mapping to delineate arm lymphatics from axillary lymphatics.

Finding the most suitable technique for each type of lymphedema with variable stages is one of the most complicated decisions for practitioners. More studies are needed to reveal the exact biology of lymphedema to ensure complete understanding of the disease and improve outcomes.

Keywords: Diagnosis, lymphedema, treatment

INTRODUCTION

Lymphedema (LE) is the accumulation of protein-rich fluid in tissues. The impaired function of lymph vessels interrupts the drainage of lymphatic system that is a part of the circulatory system just like the arterial and venous structures. Lymph vessels remove excess fluid from tissues and transport it back to the circulation. In addition, the maturation of immune cells takes place in the lymphatic system; thus, it constitutes one of the most critical defense mechanisms throughout the body. Lymph capillaries are located in the dermis, woven like a cobweb, then drain to lymphatic vessels in the subcutaneous plane and ultimately to the deeper system and the thoracic duct.

Lymphedema can either be primary or secondary. Regardless of the etiology, it is clinically characterized with chronic swelling, localized pain, atrophic skin changes and secondary infections (1). However, the main devastating aspect of LE is the appearance of the affected limb that causes psychological morbidity. Primary LE is related to developmental abnormalities of the lymphatic system whereas secondary LE is attributed to the impairment of lymphatic vessels due to an acquired condition such as trauma, tumor, surgery or infection (Table 1). In developing countries, secondary LE is mainly due to infections-infestations influencing lymphatic channels. On the other hand, in developed countries, secondary LE occurs most commonly after surgical removal of lymph nodes for cancer treatment (2). Breast cancer is the most common cancer among women in the world and Breast Cancer Related Lymphedema (BCRL) occurs more often than any other type of LE (3). This review will focus on BCRL.

Incidence

Breast Cancer Related Lymphedema is detected in 7-77% of patients who undergo axillary lymph node dissection (ALND) due to transection of lymph vessels as depicted in selected studies (4). Sentinel lymph node biopsy (SLNB) significantly reduces this risk to 3-7% (5, 6). This incidence is based on multiple factors such as extent of disease, treatment modality (i.e. radiotherapy), and duration of follow-up (6, 7). In addition to these, a study revealed that patients with occupations that require extra upper extremity activity had the worst stage and grade LE clinically (3). In another study, factors associated with the development of BCRL included occupation, infection, and increased BMI. Immediate reconstruction of the breast was not found as a risk factor for BCRL (8). A recent study reported a risk assessment tool using these BCRL predictors (RATE-L), which included significant predictors such as post-mastectomy radiation, age above 65 years, and axillary dissection (9).

Cite this paper as:
Kayıran O, De La Cruz C, Tane K, Soran A. Lymphedema: From diagnosis to treatment. Turk J Surg 2017; 33(2): 51-57

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Received: 17.03.2017
Accepted: 20.03.2017

Available online at
www.turkjsurg.com

Table 1. The etiology of lymphedema

Primary	Secondary
Congenital	Trauma
Milroy disease	Tumor
Lymphedema praecox	Surgery
Lymphedema tarda	Infection-infestation
	Post-venous thrombosis

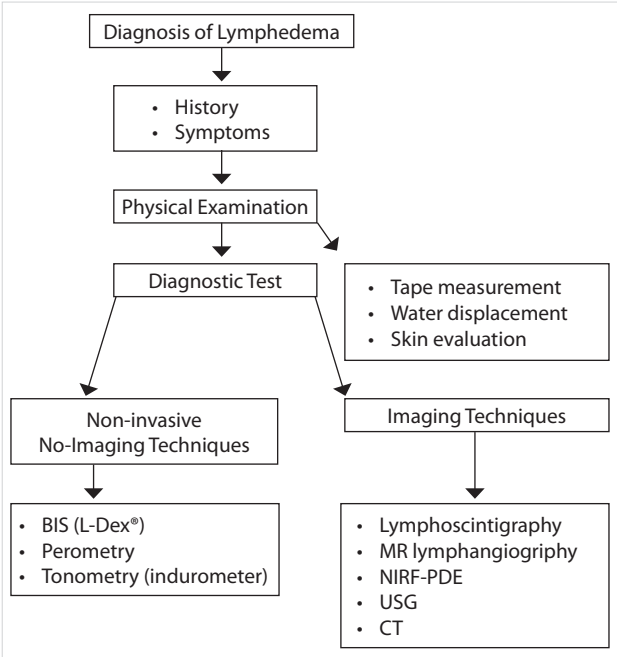

Figure 1. A scheme for the available options in the diagnosis of lymphedema
BIS: bioimpedence spectroscopy; MRI: magnetic resonance imaging; NIRF: near infra-red fluorescence imaging; PDE: photo dynamic eye (PDE; Hamamatsu Photonics K.K., Hamamatsu, Japan); USG: ultrasonography; CT: computed tomography

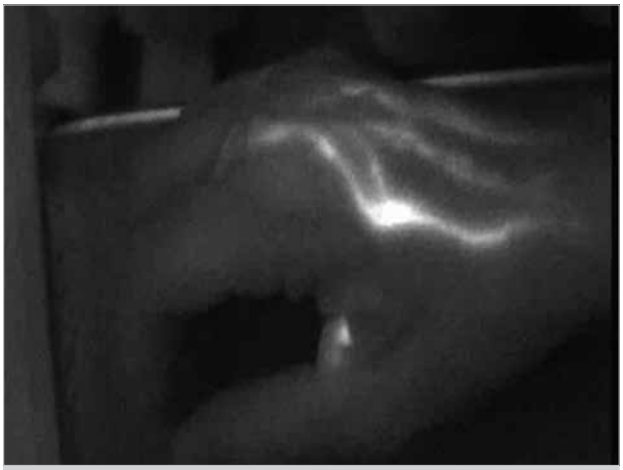

Figure 2. Near Infra-Red Fluorescence imaging (NIRF) for preoperative-intraoperative planning

DIAGNOSIS

Although there is no unique sign or criteria for defining LE, the diagnosis is usually made clinically by thorough evaluation and physical examination (2, 3, 10). Family history is important in the diagnosis of primary LE. The main symptoms are chronic swelling, progressive atrophic skin changes, and recurrent infections. It is important to identify whether the swelling is transient or persistent. In one study, it was reported that one-third of initial swelling attacks were transient (10). Since effective treatment of LE can be established in early stages, accurate and timely diagnosis is crucial (11). History of trauma or surgery must be addressed clearly. Physical examination consists of volume and shape discrepancies, and skin changes among the extremities. Figure 1 outlines the alternatives in the diagnosis of LE.

Circumferential (>2 cm) and/or volume (>200 mL) differences between the affected and non-affected extremity can be performed to confirm the diagnosis (2). Volume can be measured by tape, water displacement or perometry (Perometer; Perosystems, Wuppertal, Germany) (12). Tape measurements require formula calculations; therefore, it is recommended that the measurements should be performed by the same person at defined intervals (12). It is mainly preferred on head and neck lymphedema follow-ups. Water displacement is an accurate method that is the gold-standard for volume assessment, especially on extremities (12); however, it is not used in daily practice because it doesn't delineate the affected area. If there is an open wound, it is not feasible to use this technique. Perometry is a computer-based study that calculates the volume of the affected limb via infra-red optical electronic scanner and can demonstrate small changes, but is expensive (2).

Non-invasive measurements (tonometry, bioimpedence spectroscopy) and imaging techniques (lymphoscintigraphy, ultrasonography, computed tomography, and magnetic resonance imaging) may aid in the detection of LE. The principal mechanism of a tissue tonometer is to evaluate tissue resistance by applying compression. Skin pliability and fibrosis can be measured with a tonometer. It gives a good idea about how changes occur during LE treatment. Tissue dielectric constant and tonometry can measure skin texture and resistance (12-14). Ultrasonography, computed tomography and magnetic resonance imaging can show the presence of extra fluid within tissues (12).

Bioimpedence spectroscopy (BIS) is a new diagnostic tool to diagnose LE. It is a technique that assesses the extracellular fluid compartment before visible changes have settled (15). BIS mainly focuses on changes in electrical conductance of extracellular fluid. Since it depends on water content of the study area, advanced and fibrotic edema detected in late-stage LE may not be diagnosed properly by BIS (12). In other words, BIS is reliable in early-stage BCRL. A prospective observational study demonstrated the impact of L-Dex® (L-Dex; Impedimed, Brisbane, Australia) measurements in identification of subclinical BCRL and its use in routine clinical practice (16). L-Dex® is the score representing extracellular fluid ratio of the affected limb to the unaffected limb, and is sensitive in predicting the onset of LE up to 10 months prior to clinical diagnosis (15).

Lymphoscintigraphy is a nuclear medicine study and demonstrates slow or absent lymph flow usually in later stages of LE (12). Technetium 99m sulfur colloid is injected intradermally and the transit time to lymph node basins can be measured; however, subdermal lymphatics cannot be assessed. A new technique for imaging lymph vessels is Near Infra-Red Fluo-

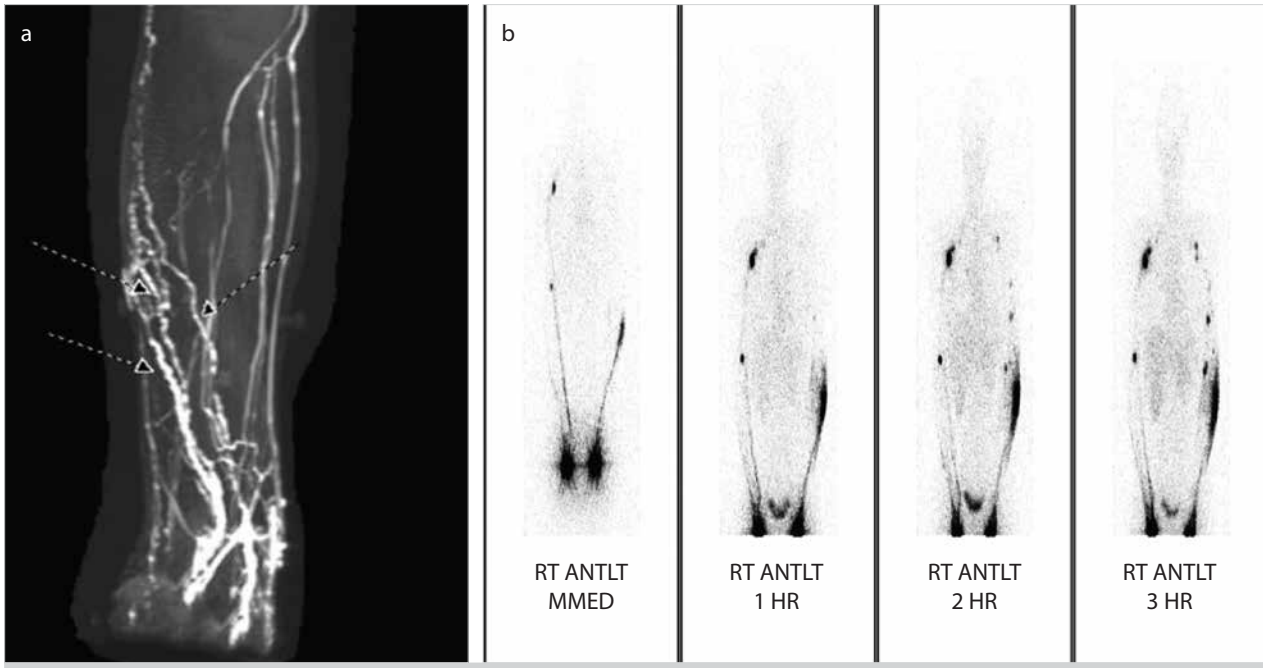

Figure 3. a, b. (a) Magnetic resonance lymphangiography. Three irregular tubular structures extending from the dorsal aspect of the wrist to the lateral/dorsal aspect of the right forearm are compatible with enlarged lymphatics. These vessels are subcutaneous and measure up to 3-4 mm in caliber. In the lateral and ventral aspect of the mid-portion of the forearm (in proximity to the expected location of two lymphovenuler anastomosis), there seems to be communication between these lymphatics and small venules, branches of the basilic and ventral branches of the cephalic vein. There is minimal dermal backflow in the lateral aspect of the mid-portion of the right forearm. (b) Lymphoscintigraphy. Abnormally delayed lymphatic transit and dermal backflow are identified in the left forearm

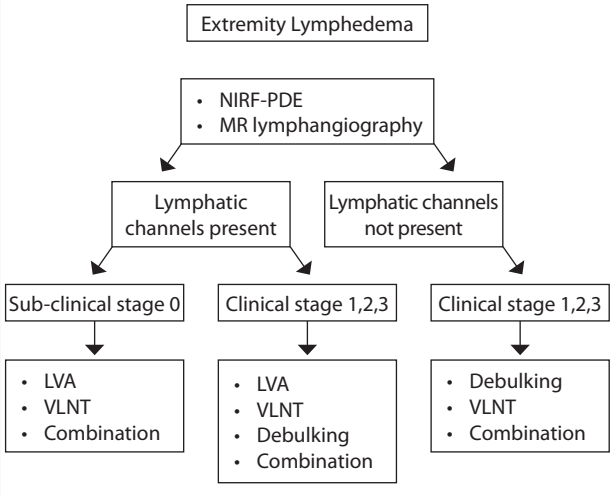

Figure 4. An algorithm for the treatment of lymphedema according to magnetic resonance lymphangiography
LVA: lymphaticovenular bypass; VLNT: vascularized lymph node transfer

Table 2. Staging of lymphedema adapted from The International Society of Lymphology

Stage	Description	Characteristics
0	Latent	Some damage to lymphatics; No visible edema yet
1	Spontaneously reversible, acute phase	Pitting edema; reversible with elevation of the arm. Usually, upon waking in the morning, the limb(s) or affected area is normal or almost normal size
2	Spontaneously irreversible, chronic phase	Spongy consistency and is "non-pitting," Fibrosis found in Stage 2 lymphedema marks the beginning of the hardening of the limbs and increasing size
3	Elephantiasis; irreversible, end-stage	Irreversible and usually the limb(s) is/are very large. The tissue is hard (fibrotic) and unresponsive; consider debulking surgey at this stage

rescence Imaging (NIRF) by using indocyanine green. This dynamic test allows visualization of superficial lymphatic flow and functioning lymphatic vessels; thus, finds abnormalities at early stages. It can be used to stage the severity of disease and for preoperative-intraoperative planning (17, 18) (Figure 2). Lymphography is another entity where radio-opaque material is directly injected into peripheral lymph vessels. This technique is rarely done due to the risk of damaging lymph vessels.

Magnetic resonance lymphangiography is a new entity that involves the injection of Gadolinium into the hand or foot to clarify the course of lymphatics. Gadolinium can also get into the venous system making the interpretation of lymphatic channels difficult (19). Magnetic resonance venogram and ferumoxytole (Feraheme; Advanced Magnetics, Cambridge, MA, USA) are used to help to differentiate lymphatics from veins (19, 20). With the advent of magnetic resonance lymphangiography, the severity of LE can be delineated while the anatomy of the lymphatic channels and the status of the soft tissues can also be depicted (20) (Figure 3). We suggested an algorithm for the management of patients with LE, by using Magnetic resonance lymphangiography and LE stage in this review (Figure 4).

Table 3. Treatment options in lymphedema

Non-surgical treatments	Surgical treatments
Complete decongestive therapy	Reductive techniques
Manual lymph drainage	Direct excision
Compression therapy	Liposuction
Exercise	Physiological techniques
Skin care	Lymphatico-lymphatic by-pass
Compression garments	Lymphatico-venous by-pass
Advanced pneumatic compression therapy	Lymph node transfer
Laser therapy	

The International Society of Lymphology classified LE into 4 stages to overcome multiple classification schemes and obtain a consensus (3) (Table 2). In addition, Campisi et al. (21) proposed a staging system consisting of 3 stages, especially for elders.

TREATMENT

The management of LE consists of accurate diagnosis, successful classification and patient education. Unfortunately, there is no absolute cure for LE. On the other hand, effective treatment is available. Two main modalities include non-surgical and surgical options (Table 3). The mainstays of non-surgical LE treatment modalities are complete decongestive therapy (CDT), compression therapy, advanced pneumatic compression pumps and exercise. These treatments are effective mainly in early-stage LE (2). There is a global trend for surgical intervention and surgical techniques including physiological and reductive methods.

Non-Surgical Treatments

Patient education is both crucial and mandatory (22). Self-care and risk-reductive practices, self-lymph drainage, skin care, proper alignment of bandages and garments, good nutrition, exercise and weight control are the basics prior to LE treatment (12).

Complete Decongestive Therapy

Complete Decongestive Therapy (CDT) is considered the gold-standard treatment method in the management of LE and includes two phases: reductive (phase 1) and maintenance (phase 2) (23). CDT is a good option in decreasing LE volume and includes manual lymph drainage, compression therapy, physical exercise, skin care as self-management, followed by wearing compression garments (23, 24). Although it is safe and effective in most patients, it is expensive, time-consuming and needs certified therapists. In addition, patient compliance to long-term CDT is challenging. Nevertheless, CDT can be individualized with modifications until the lymphedematous volume reduction has been maximized.

Manual lymph drainage (MLD): MLD is a hands-on technique and differs from standard massage by orienting the lymphedematous fluid to proper functioning lymphatics (24).

Compression Therapy: Compression therapy includes effective gradient compression with tubular bandaging on the affected limb (25). Short-stretch bandages provide low "resting pressure" when the patient is at rest and "working pressure" which allows muscle contractions to direct interstitial fluid flow (23, 25). These bandages also reduce fibrosis in the skin (25). Compression garments are different from compression bandages and are preferred in long-term treatment.

Exercise: Specific exercise is beneficial for LE patients (12). It is recommended that compression bandages or garments should be worn during activity (12). Patients with LE or people at-risk for LE are encouraged to exercise. A meta-analysis showed that active exercising reduces edema volume in BCRL (26). A recent pilot study demonstrated that yoga has beneficial effects on an individuals' posture and strength (27).

Skin Care: Establishing proper hygiene is important for patients with LE. Low pH moisturizers are recommended to overcome skin cracking and drying, in order to prevent entrance of microorganisms (12).

Compression Garments: Initial control of LE can be achieved with the use of compression bandages. Long term control is obtained with compression garments (12). The type of the garment depends on the body part. Patients should have several garments to alternate and ensure the proper pressure and hygienic control. Accurate fitted garments are essential. Some patients require additional coverage night-or-day to control or reduce LE (12).

Advanced New Generation Pneumatic Compression Therapy

Advanced Pneumatic Compression (APC) therapy can be used as an adjunct to CDT either in early or late phases (12, 28). It mimics the pump effect of muscular contraction on lymphatic system (2). Ranging between 35 and 180 mm-Hg, pump pressures are adjusted to mostly 20-60 mm-Hg (2, 12). The pressure must be individualized in order to prevent skin damage during application. APC therapy was found beneficial in reducing LE, whereas compression sleeves prevented additional swelling without influencing volume reduction (2).

Laser Therapy

A number of randomized trials have reported that Low-Level Laser Therapy (LLLT) improved measurable physical parameters as well as subjective pain scores (29). LLLT increases lymphatic drainage by stimulating the formation of new lymph vessels, by improving lymphatic motricity, and by preventing formation of fibrotic tissue (30). Usually, LLLT is used in combination with CDT. Most studies did not report any adverse events to participants, although one study stated development of cellulitis in LLLT patients as an adverse event (31). Its causal relationship to LLLT was unknown.

SURGICAL TREATMENTS

Reductive Techniques

Direct excision: These techniques include removal of lymphedematous tissue. Previously described methods such as the Charles procedure include complete removal of all subcutaneous tissue and skin grafting (32). This method, although effective at volume reduction, can be quite disfiguring. It also can require blood transfusions and lengthy wound healing. Another technique used in the past involved buried dermal flaps

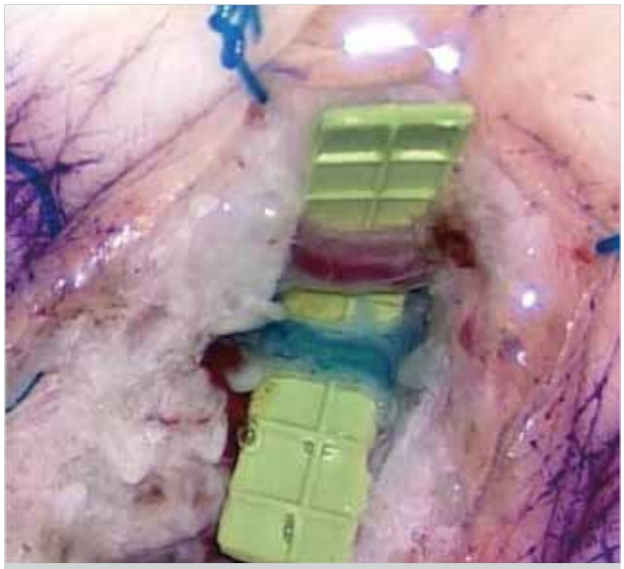

Figure 5. Lymphovenous anastomosis. Please note supermicrosurgery is used to establish such an anastomosis

with variable success (33). Direct excision techniques may involve full-thickness skin grafting (FTSG) or vacuum-assisted closure therapy (2). In extreme cases, these techniques allow for improvement in quality of life.

Liposuction: Surgical debulking of the affected extremity using liposuction has been shown to be very effective at reducing the volume to near normal (34). This technique has been used in both congenital and acquired LE. It has also been used in cases of lipedema. It has been reported that liposuction technique provides long standing reduction in extremity size as compared to the normal side (35). This technique requires patient compliance with compression therapy to prevent regression. Patients considering this technique should undergo pre-operative conservative management with no pitting edema (34). It has been shown to be effective both in the upper and lower extremity, although it is more effective in the upper extremity. It is known that adipose tissue functions as a crucial organ and a cytokine-activated cell in LE (36). The removal of adipose tissue using liposuction does not affect the already decreased lymph transport system in LE (34). Moreover, a significant improvement was detected in skin blood flow and quality of life after liposuction (37, 38). Its complications include infection, skin necrosis and recurrence.

PHYSIOLOGIC TECHNIQUES

Lymphatic venous anastomosis, lymphatico-lymphatic bypass, and lymph node transfer can be listed as physiologic methods. Many of these methods use recent developments in technology to assist in identifying lymphatic channels and lymph nodes (2, 39).

Lymphatic Venous Anastomosis (LVA) or Bypass

LVA was first described in an animal model with several human studies to follow (40, 35). This technique involves the creation of connections between the lymphatic system and the venous system in the distal or proximal extremity. Superficial or deep lymphatics are anastomosed with neighboring veins. Fluorescence is used to help identify the lymphatic system and an operating microscope is used to assist in microsurgery (41). Single or multiple LVA's have been reported by different authors using differing surgical sites (39, 42-44). Supermicrosurgery (anastomosis less than 0.8 mm vessels) is used in this technique, in which lymphatic vessels and adjacent venules are anastomosed, mostly in an end-to-end fashion (39, 43) (Figure 5). Variations on the configuration of anastomosis type were described in several studies with variable success rates (45, 46). Studies have reported improvement in patients both subjectively and objectively. In general, LVA's have been shown to be a safe technique for the management of LE (39, 43).

Vascularized Lymph Node Transfer: Vascularized lymph node transfer was first introduced in animal models (47). It has recently been applied to humans with gaining popularity. There are different options for lymph node transfer, namely the location of the donor and the recipient sites. Options for lymph node harvest include the lateral thoracic region, groin, submental region, supraclavicular region and intraabdominal lymph nodes (44, 48, 49). Each donor site has its particular anatomic advantages and disadvantages, and contains varying number of lymph nodes ranging from 1-10. The lymph nodes can be harvested together with a portion of the skin if necessary. These operations require microsurgical skills to perform an arterial and venous anastomosis to provide blood supply to the transferred tissue. The results of lymph node transfer are quite promising and have been shown to provide both objective and subjective improvements (35).

One consideration for lymph node transfer is the concern for possible LE at the donor site (50). Reverse lymph node mapping, originally described as a technique to refine axillary dissection, can be used to minimize lymph node harvest related morbidity (51). It allows differential identification of nodes which drain the neighboring extremity in addition to the ones that are included in the tissue to be removed. Reverse lymph node mapping involves the use of the photodynamic eye, Technetium and ICG dye. Using this technique, the surgeon can be reassured that no lymph nodes are removed that drain the extremity (51). Clinically, the benefit of lymph node transfer is to restore immunologic function to the extremity and improve fluid drainage. However, the action mechanism of lymph node transfers is poorly understood. The transferred nodes have been shown to be active in a number of studies. One proposed mechanism suggests that the new lymph nodes act as "pumps" which filter the surrounding fluid (52). The best site for lymph node implantation is currently unknown. In some cases, the nodes have been placed distally whereas in others they were implanted proximally (52). Well-designed controlled prospective studies are needed to clarify if the suggested functional surgical methods are beneficial in the long-term.

A variety of lymph node transfers includes a tissue portion to be transferred with lymph nodes. Such examples include transferring the lower abdominal tissue in case of total breast anatomical reconstruction (TBAR) and latissimus dorsi flaps with lymph nodes. In such cases, both the breast and the lymph nodes are reconstructed (44, 50, 53). Other types of flaps such as those harvested intraabdominally carry lymphatic tissue from the omentum (49). These can be harvested either by open surgery or laparoscopically.

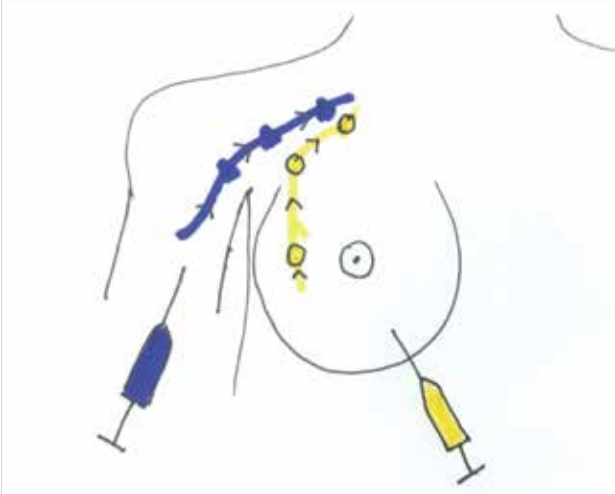

Figure 6. The mapping of axillary lymphatics. A radioisotope is injected into the breast, whereas blue-dye is administered subcutaneously to the upper arm. The lymphatic flow of the breast and arm is separately revealed

Intraoperative Considerations

The nodal status defines one of the most important prognostic factors in breast cancer. However, although necessary, axillary dissection may compromise the lymphatic system thus contributing to the development of LE.

Recently, the lymphatic drainage of the arm and breast tissue were studied and it was found that preserving arm lymphatics during SLNB and/or ALND via a new concept called axillary reverse mapping (ARM) may reduce the risk of BCRL (4, 54, 55). ARM is based on the hypothesis that drainage of arm lymphatics differs from that of breast lymphatics (4, 54). However, it was shown that lymphatic interconnections exist in the axilla between arm and breast lymphatics (56). The technique of mapping the arm and breast lymphatics is comprised of radioisotope injection to the breast and blue dye injection to the upper arm (Figure 6). The lymphatic pathways and interconnections are determined. When a crossover is identified, blue nodes should be removed (55). ARM reduced BCRL when compared with conventional breast cancer surgeries, nevertheless, randomized controlled studies are needed (55).

CONCLUSION

Breast Cancer Related Lymphedema is a devastating disease affecting millions of women. Its treatment is aimed at curing the disease and reducing recurrence rate. However, treatment methods create both physical and psychological morbidity to the patients. BCRL influences daily activities and affects patient self-esteem in various ways. Modern surgical and non-surgical techniques offer numerous methods for the patients to overcome BCRL. In the future, we hope to ensure 100% success in the control or elimination of BCRL. Until then, the exact biology, pathogenesis of lymphatic system diseases and the treatment options require further research to be able to understand this devastating disease.

Peer-review: Externally peer-reviewed.

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

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

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

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Turk J Surg 2017; 33: 58-61
DOI: 10.5152/UCD.2017.3182

A complication of thyroidectomy: Do not forget suture reaction

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ABSTRACT

Objective: In this study, we aimed to present patients who have developed suture reaction and were treated in our clinic following thyroidectomy operation.

Material and Methods: Patients who had been treated for suture reaction following thyroidectomy between January 2012 and December 2014 were retrospectively evaluated. The patients were analyzed in terms of their age, gender, duration of the symptoms, type of previous operation and treatment modality.

Results: Between January 2012 and December 2014, 559 thyroid/parathyroid operations were performed in our clinic. A total of 12 patients were admitted with suture reaction within this period thus yielding a suture reaction incidence of 2.1%. The mean age of these patients was 42±7.65 years, 75% of them were female while 25% of them were male. The types of previous operations were bilateral total thyroidectomy in 83.3%, lobectomy in 8.3% and near total thyroidectomy in 8.3% of the patients. The mean symptom duration was 7.2±4.3 (2-16) months. Two patients (16.7%) underwent a second surgical operation for suture reaction, while 10 patients (83.3%) were treated conservatively. None of the patients developed complications.

Conclusion: One of the most common complications that develop after thyroidectomy is bleeding. Ligation must be performed in order to prevent this complication. As it is known, surgical ligation with sutures may cause tissue reaction. Sutures that are absorbable and have a low risk for reaction formation should be chosen if suturing is preferred.

Keywords: Complication, fistula, sutures, thyroidectomy

INTRODUCTION

Thyroid surgery has historically been an adventure for surgeons until a century ago when several advances leading to modern surgery have been made, especially after Emil Theodor Kocher (Swiss doctor, medical researcher). In parallel with medical technologic developments and increased surgical experience, currently, surgery with low rates of mortality and morbidity has become a procedure of choice (1, 2).

Although there are many complications which may be encountered by thyroid surgeons, the most serious ones are recurrent laryngeal nerve injury, permanent hypoparathyroidism and postoperative bleeding. In thyroid surgery, re-operation is rarely needed in the presence of conditions such as early postoperative hematoma, recurrence, and those requiring completion thyroidectomy (3).

One of the most common complications seen after thyroidectomy is bleeding. Ligation must be performed for preventing this complication. Many surgeons prefer conventional suturing. As it is known, sutures are foreign bodies for the body and may cause a reaction, which is more common especially with non-absorbable sutures (1, 4, 5).

In this study, our patients who were treated for suture reaction following thyroidectomy were presented.

MATERIAL AND METHODS

In this study, the patients who were treated for suture reaction following thyroidectomy in Elazığ Training and Research Hospital, Health Sciences University, Turkish Ministry of Health, General Surgery Inpatient/Outpatient Clinic between January 2012 and December 2014 were retrospectively evaluated. The study data were obtained from patient files, discharge reports, outpatient clinic records, personal registration forms of the authors and computer records. The patients with missing data and those who underwent thyroidectomy in another center were excluded. Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research

Cite this paper as:
Kanat BH, Bozan MB, Emir S, Yazar FM, Erol F, Alataş Ö, Altınsoy HB, Aksu A. A complication of thyroidectomy: Do not forget suture reaction. Turk J Surg 2017; 33(2): 58-61

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Received: 28.04.2015
Accepted: 04.10.2015

Available online at
www.turkjsurg.com

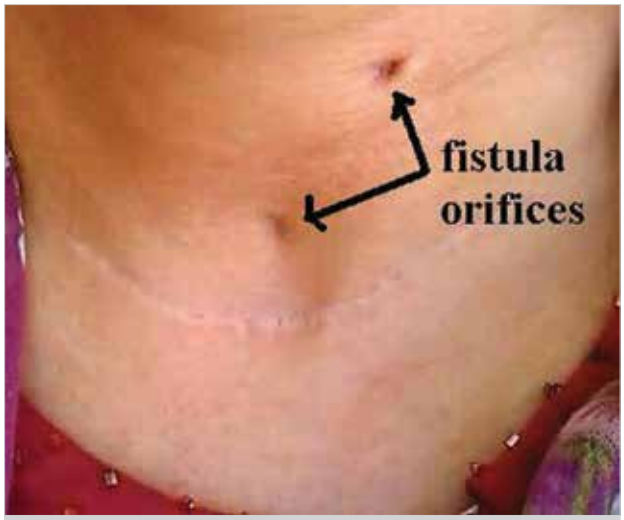

Figure 1. Patient with swelling and fistula in the neck

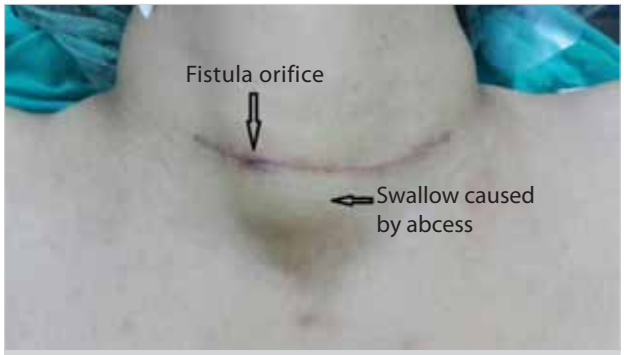

Figure 2. A tender fluctuating neck swelling under the incision scar

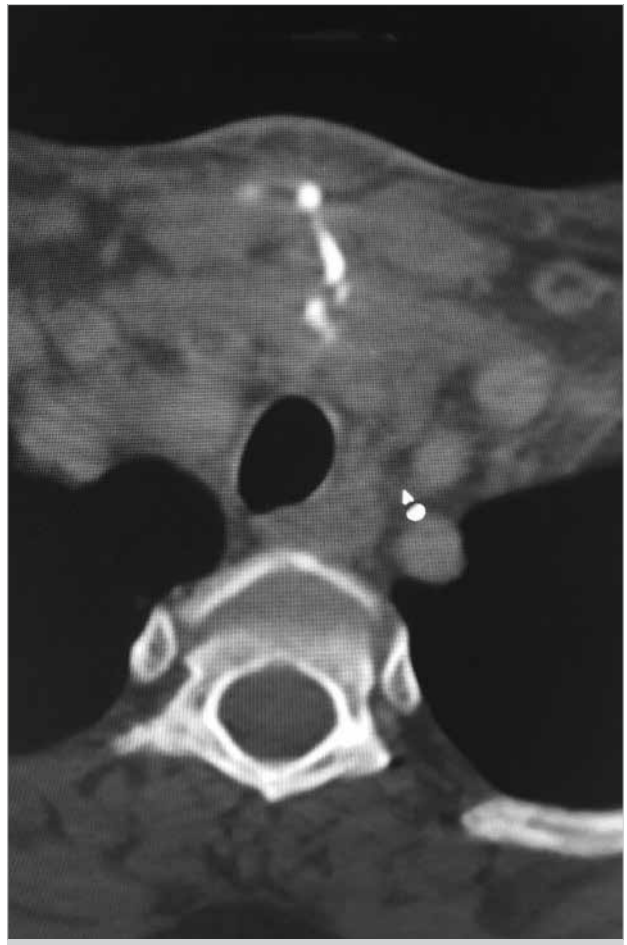

Figure 3. CT view of the fistula tracts extending from the incision line to the trachea

committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The diagnosis of suture reaction was made by physical examination of the patients with a history of thyroidectomy, and discharge, swelling and fistula in the neck (Figure 1). Imaging methods were used in the presence of suspicion. Conservative treatment was applied by opening the fistula tract and removing suture materials from this tract under local anesthesia, while surgical treatment was performed by excising the fistula tract and suture materials under general anesthesia.

The patients were analyzed in terms of their age, gender, duration of the symptoms, type of previous operation and treatment modality. The data analysis was performed using the Statistical Package for the Social Sciences for Windows version 12.0 (SPSS Inc.; Chicago, IL, USA).

RESULTS

Between January 2012 and December 2014, a total number of 544 thyroid operations, which consisted of bilateral total thyroidectomy in 501, lobectomy in 18, unilateral total-contralateral subtotal thyroidectomy in 6, and near total thyroidectomy in 19 cases. Additionally, 15 parathyroid operations (concurrent with the thyroid operation in 7 cases) were performed.

During this period, a total of 14 patients were admitted with a diagnosis of suture reaction. Since one of these patients had been operated in another health center and another one had been operated before January 2012, these two patients were excluded, and 12 patients were enrolled in the study. The incidence of suture reaction for the patients who were operated during this period was found to be 2.1%.

The mean age of the patients was 42±7.65 (24-51) years, 75% of them were female while 25% of them were male. The types of previous operations were bilateral total thyroidectomy in 83.3%, lobectomy in 8.3% and near total thyroidectomy in 8.3% of the patients. The mean symptom duration was 7.2±4.3 (2-16) months. Two patients (16.7%) underwent a second surgical operation for suture reaction, while 10 patients (83.3%) were treated conservatively. None of the patients developed postoperative complications. The patients except the ones who underwent surgery were not hospitalized.

In the physical examination of one of the patients treated by surgery, there was a tender neck swelling under the incision scar, which was fluctuating especially at the right (Figure 2). The patient was evaluated with the suspicion of hematoma, infection and foreign body reaction. The ultrasound examination revealed heterogeneity of 3 cm in size and edema between tissues. A computerized tomography (CT) was recommended by the department of radiology due to the presence of a suspicious hypoechoic line extending from the incisional line to the trachea. Contrast agent was given into the tract after cannulation of the tract while obtaining the CT scan.

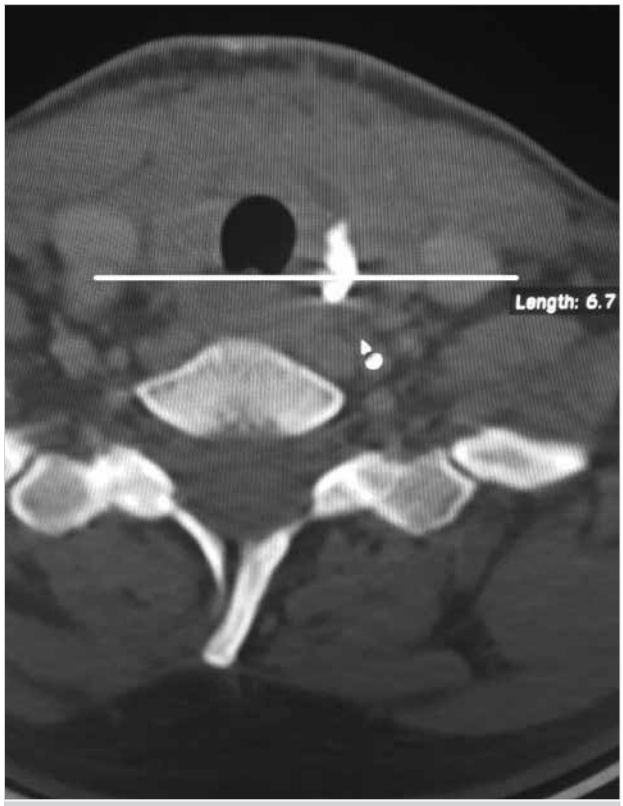

Figure 4. CT view of fistula tracts extending from the incisional line to the trachea

On CT, fistula tracts extending from the incision line to the trachea and both lobes of the thyroid gland were detected (Figure 3, 4). The abscess was drained after opening the fistula tract under general anesthesia. The fistula tract was excised and the sutures causing foreign body reaction were extracted from both thyroid lobes adjacent to the trachea.

In the other patient treated surgically, differentiation of foreign body and recurrence could not be made by imaging techniques. The patient was operated with the suspicion of a foreign body. Abscess in the left lobe and 8 to 10 suture materials were detected in the same site, the area was cleaned.

DISCUSSION

Thyroidectomy is the most commonly performed endocrine operation in surgical clinics. One of the most common complications seen after thyroidectomy is bleeding. For this reason, all surgeons do their best to provide an effective bleeding control (3, 6).

Bleeding control is one of the indispensable factors of surgery. Ambroise Paré (the most important surgeon of the 16th century who is accepted as the father of surgery in France) is the first physician to report that hemostasis could be easily achieved by vessel sealing (7, 8). Although this method has been introduced in the middle age, thyroid surgery has not been performed routinely until the 1900s due to high bleeding rates (4).

Better vascular bleeding control has been achieved by the developments in surgical tools and techniques. Fundamental changes in the approaches of surgeons to vascular bleeding control have occurred especially due to new vessel sealing devices, which were introduced in the last decade. It has been reported that the endurance of these devices are equal to that of clips and knots if the devices were used in appropriate capacity (4, 9)

In a questionnaire study on thyroid surgery and vessel sealing devices performed in our country, it was found that these devices are used in 65% of all thyroidectomy operations. In the same study, 47% of the surgeons reported that they use ligation in every case, while 55% stated that upper pole vessels must be ligated at least once (4).

Surgical ligation is achieved by using sutures. As it is known, all sutures are foreign bodies for the body and cause tissue reaction. Tissue reaction continues until the sutures are totally absorbed when an absorbable suture is used, while fibrous capsule formation is observed with the use of non-absorbable sutures. However, the body may sometimes develop an excessive reaction against this foreign body (10-12).

In our clinic, we use vessel sealing devices in the majority of dissection stages of thyroidectomy operations. However, we especially ligate upper pole vessels and structures close to the recurrent laryngeal nerve with sutures. In the previous years, non-absorbable silk sutures were used for ligating while absorbable sutures are currently being preferred. In our series, silk sutures have been used and the reactions occurred against silk. Similar cases have been reported in the literature. In the studies performed in our country, post-thyroidectomy suture reaction rate was determined as 0-1.3%, while this rate was found as 2.1% in our study, being higher than that reported in the literature (13-15).

In the literature, the treatment methods used in these cases was unclear. In case of reaction, a chronic fistula usually develops and the suture material is removed from the tract spontaneously or by a minor surgical procedure. We usually perform such interventions under local anesthesia. However, surgical intervention was performed under general anesthesia in two cases due to the extensive and deep reaction in one of them and suspicion of a foreign body (sponge) in the other.

A suitable suture material should be easy to use, cheap and compatible with the tissue with a minimal tissue reaction. However, a suture material meeting all these criteria is yet not present. Silk is a proteinous material produced by silkworm. Therefore, it causes a significant inflammation in tissues. For this reason, it should be remembered that reaction may develop against silk suture material (16, 17).

Vessel sealing systems and ligation techniques with conventional sutures may be used in the dissection stages of thyroidectomy. Many studies in the literature have compared these two techniques, and no superiority has been detected in terms of efficiency. However, some studies indicated superiority of vessel sealing systems in terms of operation time as compared to conventional hemostasis techniques in thyroid surgery, with no detriment to safety outcomes (18). Sutures with a low risk for reaction and especially absorbable sutures should be preferred especially for upper pole ligation, as in our practice.

CONCLUSION

Vessel sealing systems or classical suturing may be used during dissection in thyroidectomy. Development of suture reaction should be considered when suturing is preferred. It must be remembered that suture reaction may develop in conventional suturing. In such a condition, conservative treatment should be the primary choice.

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 - B.H.K., F.M.Y., S.E.; Design - B.H.K., M.B.B., F.M.Y., S.E.; Supervision - M.B.B., B.H.K., F.M.Y.; Resource - M.B.B., F.M.Y., B.H.K., Ö.A., H.B.A.; Materials - F.M.Y., B.H.K., Ö.A., H.B.A.; Data Collection and/or Processing - F.E., A.A., Ö.A., H.B.A.; Analysis and/or Interpretation - B.H.K., M.B.B., F.M.Y.; Literature Search - A.A., Ö.A., F.E., M.B.B., Writing Manuscript - B.H.K., M.B.B., S.E.; Critical Reviews - F.M.Y., S.E., B.H.K., M.B.B.; Other - A.A., Ö.A., H.B.A.

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

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

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Turk J Surg 2017; 33: 62-68
DOI: 10.5152/turkjsurg.2017.3337

Preventing oxygen free radical damage by proanthocyanidin in obstructive jaundice

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ABSTRACT

Objective: Tissue damage and endotoxemia in obstructive jaundice are attributed to the increase in oxygen free-radicals. We aimed at evaluating the possible protective effect of grape seed proanthocyanidin extract (GSPE), which is a potent exogenous free-radical scavenger and antioxidant.

Material and Methods: The study was performed at the Necmettin Erbakan University Meram School of Medicine Research and Application Center for Experimental Medicine Laboratory with ethical approval. 30 Wistar-Albino rats were used and were divided into 3 groups. The common bile duct was identified and only dissected in the first group (sham). Following dissection of the common bile duct it was ligated with 4/0 silk just above the pancreas in the second group (control). After ligation of the common bile duct, 100mg/kg/day GSPE was administered via orogastric lavage for 10 days in the third group.

Results: Biochemical values revealed a statistically significant difference between Group I and the others. There was no difference between Group II and III regarding biochemical values. There was a statistically significant difference, however, between Group II and III with regards to nitric oxide levels. There was a statistically significant difference between Group I and the other groups concerning hepatic and pulmonary tissue damage on histopathologic evaluation. There was no difference among the groups with regards to renal tubular damage.

Conclusion: Proanthocyanidin is an effective natural antioxidant in decreasing the level of tissue damage caused by oxygen free-radicals.

Keywords: Antioxidant, jaundice, proanthocyanidin

Cite this paper as:
Savdan M, Çakır M, Vatansev H, Küçükkartallar T, Tekin A, Tavlı Ş. Preventing oxygen free radical damage by proanthocyanidin in obstructive jaundice. Turk J Surg 2017; 33(2): 62-68

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This study was presented at the 51st Congress of the European Society for Surgical Research, 25-28 May 2016, Prague, Czech Republic.

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Received: 16.08.2015
Accepted: 19.10.2015

Available online at
www.turkjsurg.com

INTRODUCTION

The condition caused by the obstruction of extrahepatic bile ducts for any reason is called obstructive jaundice. This condition generally needs to be treated surgically. Major complications like sepsis, renal failure, and pulmonary dysfunction are frequently seen in these patients. The toxic effects of elevated levels of bile salt and bilirubin in the cell cause local damage, while the released mediators result in systemic complications (1). These alterations lead to hepatocyte damage, portal and systemic endotoxemia, liquid electrolyte loss, and malnutrition (1, 2). It has been reported that tissue damage and endotoxemia related to obstructive jaundice causes an increase in the production of oxygen free-radicals which in turn increases lipid peroxidation (3, 4).

Oxygen free radicals impair both the cellular membrane and intracellular structures. Antioxidant materials with decreased secondary intestinal absorption and decreased plasma levels cause failure in fat absorption and increase oxidative damage in obstructive jaundice (5, 6). Oxidant damage and lipid peroxidation aggravate the already existing hepatic damage in obstructive jaundice (7, 8).

Proanthocyanidins, which are potent natural antioxidant compounds, are found in dried nuts and fruits, seeds, vegetables, fruits, and barks. Proanthocyanidins refer to a specific group of flavonoids that are polyphenolic compounds. Proanthocyanidins demonstrate their free-radical scavenger and antioxidant activity through vasodilator, anti-carcinogenic, anti-allergic, anti-inflammatory, antibacterial, cardio-protective, immune-stimulant, antiviral, estrogenic effects related to cyclooxygenase, phospholipase A2, and lipooxygenase inhibition (9-11).

In this experimental study, we aimed at evaluating the possible protective effect of grape seed proanthocyanidin extract (GSPE) which is a potent exogenous free-radical scavenger and antioxidant.

MATERIAL AND METHODS

The study was carried out at the Research and Application Center for Experimental Medicine Laboratory of Necmettin Erbakan University with the consent of the ethical board (31.10.2012-2012/86). 30 Wistar-Albino rats weighing approximately 200-250 gr were used in the study. The animals were fed with unlimited standard rat feed and tap water during the course of the experiment. Five rats were placed in each cage

and after they got adapted to laboratory conditions, they were randomly divided into 3 groups of 10 rats.

Anesthesia and Surgical Procedure: In all surgical procedures anesthesia was secured through intraperitoneal administration of 100 mg/kg ketamine HCI (Ketalar vial; Parke-Davis, Morris Plains) and 25 mg/kg Xylazine HCI (Rompon vial, Bayer). Following anesthesia, the abdominal areas of all animals were shaved. The abdominal area was cleaned with 10% povidone iodine. Laparotomy was performed with a 3 cm mid-line incision. The common bile duct was identified and only dissected in the first group (sham group). Following dissection of the common bile duct, it was ligated with 4/0 silk just above the pancreas in the second group (control group). After ligation of the common bile duct, the rats were administered 100 mg/kg/day GSPE through orogastric lavage (under anesthesia) for 10 days in the third group (treatment group). The abdominal wall of all groups were closed with 3/0 polyglactin sutures.

Sampling: All animals were sacrificed by high dose anesthetic material at the end of day 10. Following laparotomy and sternotomy, 5 cc of blood was drawn from the heart for biochemical analysis and tissue samples were obtained from the liver and kidneys for pathologic evaluation.

Biochemical Analysis: Total bilirubin (T.Bil), direct bilirubin (D.Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), urea, creatinine, serum nitric oxide (NO), and malondialdehyde (MDA) levels were analyzed. Blood samples were analyzed by Olympus/AU 5200 (Konsesyum, Alternative Biomedical Services, Dallas, TX, USA). Serum nitric oxide (NO) measurements were carried out by ELISA method using nitric oxide colorimetric assay kits. MDA measurements were manually conducted by Perkin Elmer lambda 25/UV-Vis spectrometers.

Pathologic Evaluation: All tissues were placed in 10% formalin solution for 24 hours for fixation. Tissue tracking procedure was carried out for 16 hours in an autotechnicon processor (Leica ASP300). 5µm-wide sections were obtained from tissues buried in paraffin blocks using microtome knives onto lysine slides. The samples were stained with hematoxylin eosin. The preparations with completed staining were evaluated by a single pathologist using Olympus BX51 light microscope. The tissues were scored according to the following features.

For the Lungs: A tissue damage evaluation scale was used as was stated in an article by Özdülger et al. (12). In this scale:

Grade 1 refers to normal pulmonary histology,

Grade 2 to mild neutrophil leukocyte infiltration,

Grade 3 to moderate neutrophil leukocyte infiltration, perivascular edema formation, partial destruction in pulmonary structure, and

Grade 4 refers to intensive neutrophil leukocyte infiltration, total destruction in pulmonary structure.

For the Kidneys: Granulovacuolar degeneration and widening in renal tubules were evaluated in 5 grades semi-quantitatively as stated by Chen et al. (13): Grade 1: No renal tubule damage, Grade 2: Renal tubule damage >25%, Grade 3: Renal tubule damage 25-0%, Grade 4: Renal tubule damage 50–75%, Grade 5: Renal tubule damage 75–100%.

For the Liver: Microabscess caused by cholestasis, widened bile canaliculi, necrosis located in the portal area in the liver were evaluated by light microscopy. The evaluation of bile infarctions and portal area necrosis was carried out according to the largest necrosis area and the size of the biliary infarct area (14): Grade 1: No biliary infarction and necrosis, Grade 2: The size of the biliary infarction and necrosis is smaller than 1 large enlargement field, Grade 3: The size of the biliary infarction and necrosis is equal to 1 large enlargement field, Grade 4: The size of the biliary infarction and necrosis is larger than 1 large enlargement field.

Statistical Analysis: The data collected within the framework of this study was evaluated by Statistical Package for the Social Sciences SPSS 15.0 package program (SPSS Inc.; Chicago, IL, USA). Following the execution of the normality test, the differences among groups were studied and non-normally distributed variables in binary groups were studied by the Mann-Whitney U test, while those with normal distribution were evaluated by the Student T test.

While evaluating the differences among the groups, significance level was set at 0.05 and in cases where $p<0.05$ it was stated that there was a significant difference among groups while in cases where $p>0.05$ it was expressed as no significant difference among groups.

RESULTS

There was a decrease in daily food and water consumption in the control and treatment groups. Weight loss and tardiness in movement was observed in the groups with obstructive

Table 1. Biochemical parameters

Parameters	Group 1	Group 2	Group 3
Total bilirubin (mg/dL)	0.11±0.00[a,c]	13.84±4.84	12.72±5.10
Direct bilirubin (mg/dL)	0.10±0.00[a,c]	9.92±3.26	9.31±3.80
AST (U/dL) 799.71±303.95	237±37.41[a,c]	906.7±461.51	
ALT (U/dL) 175.86±66.91	64.75±16.40[a,c]	172.29± 116.04	
ALP (U/dL)	117.5±39.8[a,c]	307.5±144.5	363.1±107.3
GGT (U/dL)	4.0±0.00[a,c]	20.14±9.35	24.14±8.15
Urea (mg/dL)	87.6±3.31	47.88±3.81	44.54±3.71
Creatinine (mg/dL)	0.43±0.02[a,c]	0.34±0.37	0.2±0.22
NO (mmoL/L)	1.45±0.05[a,c]	4.92±0.43[b]	3.62±0.36
MDA (µM/mg prot)	11.70±0.88[a,c]	19.48±3.22[b]	20.1±2.97

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase; NO: nitric oxide; MDA: malondialdehyde; SD: standard deviation
Values are presented as mean±SD
[a]: group 1 vs group 2 ($p<0.05$)
[b]: group 2 vs group 3 ($p<0.05$)
[c]: group 1 vs group 3 ($p<0.05$)

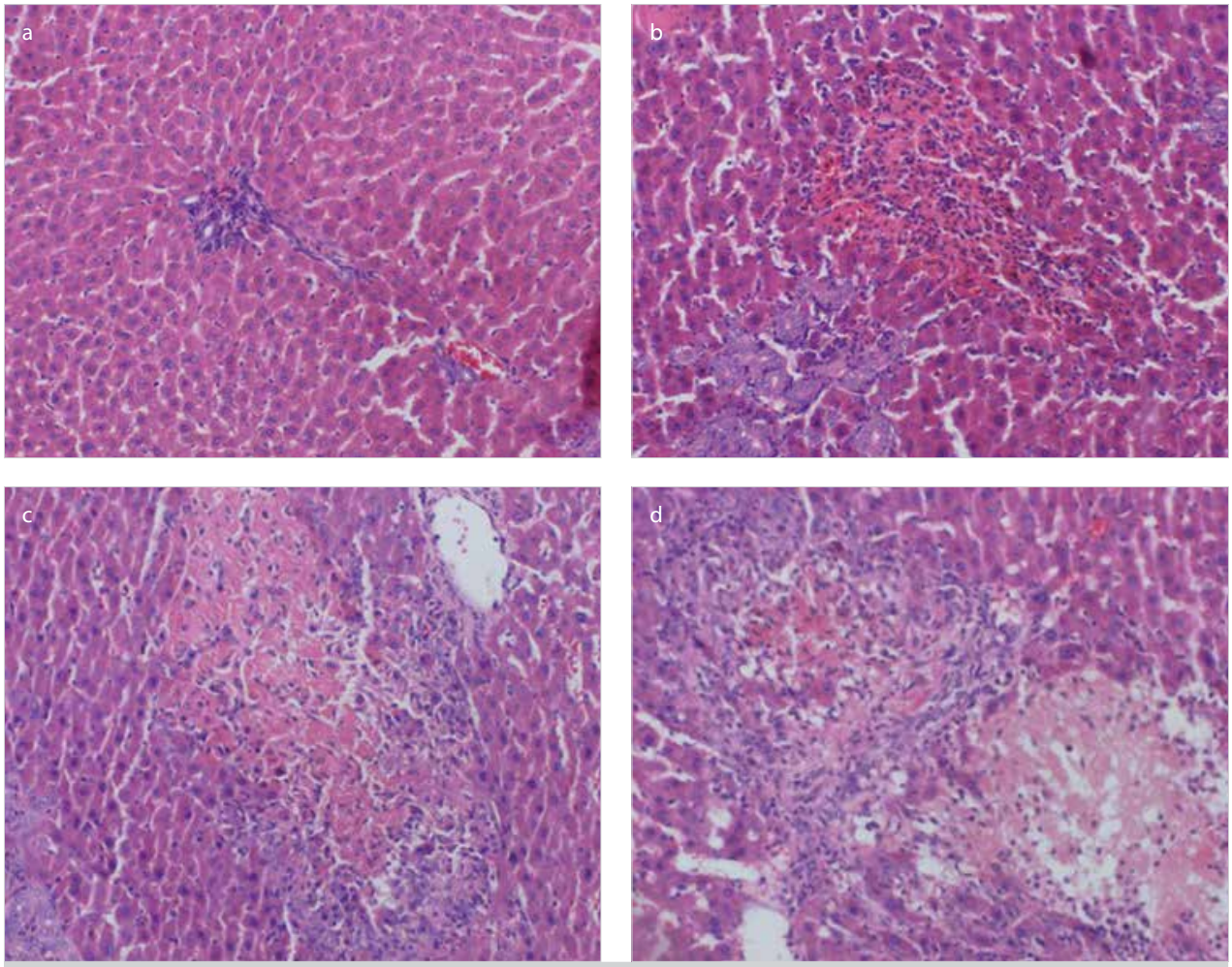

Figure 1. a-d. Hepatic histopathologic views. (a) normal (group 1), (b) grade I (group 1), (c) grade II (groups 1-3), (d) grade III (groups 2-3) damage. The necrosis and microabscess shown are related to cholestasis (hematoxylin and eosin x40)

Table 2. Histopathologic evaluation results

Histopathologic changes	Group 1 (%)			Group 2 (%)			Group 3 (%)		
	Liver [a,c]	Kidney	Lung [a,c]	Liver [a,b]	Kidney	Lung [a,b]	Liver [b,c]	Kidney	Lung [b,c]
Grade 1	60	30	50	0	0	0	0	0	0
Grade 2	40	70	50	0	0	0	20	20	50
Grade 3	0	0	0	30	40	40	60	50	50
Grade 4	0	0	0	70	40	60	20	30	0
Grade 5		0			20			0	

Values are presented as %.
a: Group 1 vs Group 2 ($p<0.05$)
b: Group 2 vs Group 3 ($p<0.05$)
c: Group 1 vs Group 3 ($p<0.05$)

jaundice. The re-laparotomy revealed only intraabdominal adhesions in the sham group. In addition to intraabdominal adhesions, there was edema in the liver and kidneys as well as gallbladder hydrops in the control and treatment group rats. Any macroscopically significant change was not detected in the lungs.

Biochemical evaluation revealed a statistically significant difference between Group I and other groups. There was no difference between Group II and III in terms of biochemical parameters. There was, however, a statistically significant difference between Group II and III with regards to the NO value (Table 1).

Results of Histopathologic Evaluation: There was a statistically significant difference between Group I and the others regarding hepatic and pulmonary damage ($p<0.05$) (Figure 1, 2). There was no difference among the groups in terms of renal tubular damage ($p>0.05$) (Figure 3). While there was a significant difference between Group II and III regarding hepatic and pulmonary damage, but no difference was detected between these two groups in terms of renal damage. All histopathologic findings are summarized in Table 2.

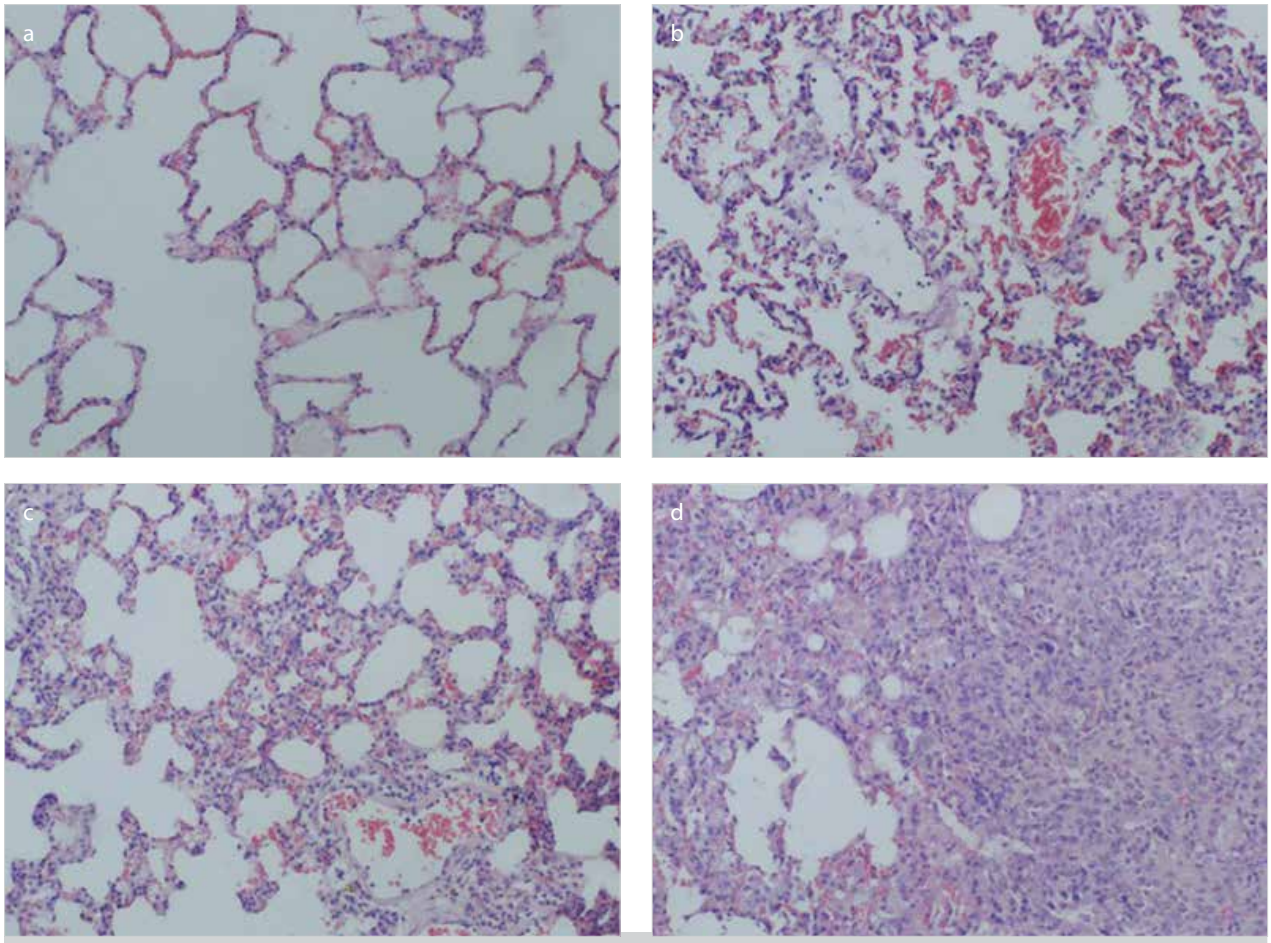

Figure 2. a-d. Pulmonary histopathologic views. (a) grade I (group 1), (b) grade II (groups 1-3), (c) grade III (groups 2-3), (d) grade IV (group 2) damage (hematoxylin and eosin, x100)

DISCUSSION

Obstructive jaundice is related to the impairment of bile flow from the liver into the gastrointestinal system due to obstruction in the intra- and extra-hepatic bile ducts. Major hepatic complications of prolonged obstructive jaundice include cholangitis, coagulation defects, biliary fibrosis and cirrhosis as a result of progressive hepatic damage. Complications such as sepsis, renal failure, and pulmonary dysfunction are frequently seen in patients with obstructive jaundice in the post-operative period (15). The toxic effects of elevated intracellular bile salts and bilirubin lead to portal and systemic endotoxemia, fluid-electrolyte imbalances, and malnutrition (2). Alterations in intestinal flora, intestinal mucosal barrier, and the immune system can be observed since flow of bile to the intestine is blocked (2). There is a correlation between high serum bilirubin levels and operative mortality in patients with jaundice (16). The most important two factors for morbidity and mortality in the post-operative period for bile duct procedures in patients with obstructive jaundice are sepsis and renal failure (17). Other conditions that arise in obstructive jaundice are the disorder in the balance of hepatic oxidative antioxidant systems and the increase in lipid peroxidation (3, 18). The gradual increase in the number of recent studies suggests that prevention of oxidative stress can play a significant role in preventing cholestatic hepatic damage. In a study on the effects of antioxidants in bile duct obstruction, Kawada et al. (19) stated that there was a disorder in the functions of hepatic stellate and Kupffer's cells in rats. In that study resveratrol, quercetin, and acetylcysteine have improved the scope of the damage caused by the regulatory functions of these two cells. This effect was associated with the antioxidant features of the agents used. Based on this, we investigated the effects of proanthocynidin, which is a potent antioxidant, on obstructive jaundice.

For the last 2-3 decades, it has been known that oxygen free-radicals (OFR) play a role in several pathologies including cancer (20). OFR are produced by parenchymal, endothelial and inflammatory cells. Their cytotoxic effects emerge when their levels are elevated and they are released out of the cell. The decrease in oxygen free-radical levels also lead to a decrease in tissue damage and accelerate healing (20). If oxidants surpass certain levels or if antioxidants prove to be insufficient, that is if the balance is lost; then protein, lipid, carbohydrate, nucleic acid, and enzymes, which are the structural elements of the organism, are impaired. In many diseases, elevated levels of reactive oxygen radicals (ROR) are not the main cause of the disease. They, however, are formed secondary to the primary disorder and subsequently play a part in pathogenesis (21). Proanthocyanidins are natural, potent antioxidant substances (22). Their antioxidant properties are very strong, Bagchi et al. (10) reported that they were stronger than Vitamin C, Vitamin E, and β-carotene (23). The inhibition level of the superoxide anion and hydroxyl radical by 100 mg/L concentration of grape seed proanthocyanidin extract was found to be 78%

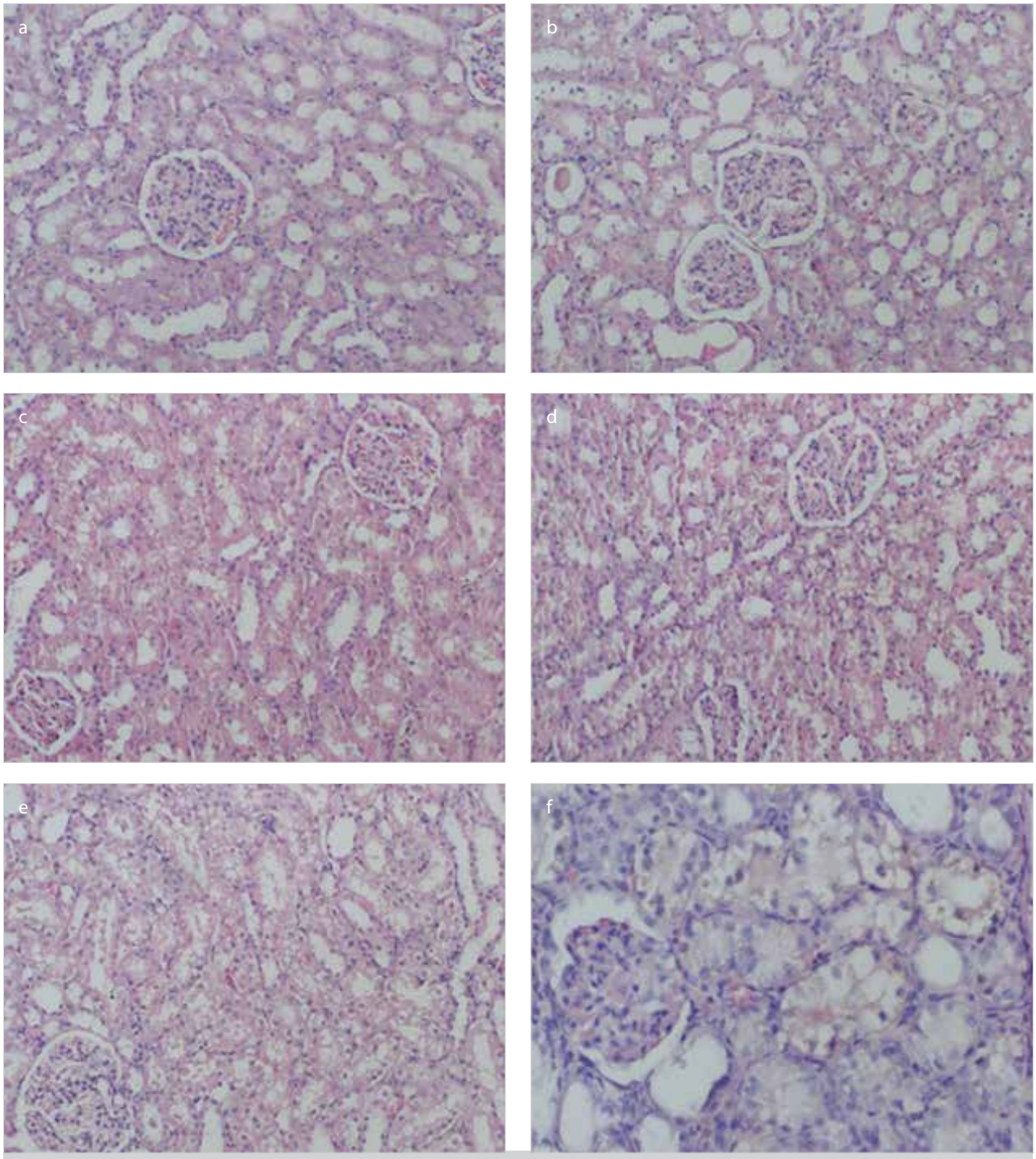

Figure 3. a-f. Renal histopathologic views. (a) grade I (group 1), (b) grade II (groups 1-3), (c) grade III (groups 2-3), (d) grade IV (Group 2-3), and (e, f) grade V (group 2) damage
(Figure a-e: hematoxylin and eosin x100, Figure f: hematoxylin and eosin x200)

and 81%, respectively. It yielded a better antioxidant effect than same dosage of Vitamin C (12% vs 19%) or Vitamin E (36% vs 44%) (22). Furthermore, proanthocyanidin has also been reported to have anti-carcinogenic, anti-inflammatory, anti-bacterial, anti-viral, cardioprotective, and immune system stimulant properties by inhibiting phospholipase A2, cyclooxygenase, and lipooxygenase enzymes (22, 23). When the MDA and NO levels, which show lipid peroxydation following obstructive jaundice, were compared it was found in our study that both parameters were significantly low in the sham group. However, there was no statistically significant difference in MDA levels of the treatment group in comparison to the control group. There was significant difference in the treatment group in comparison to the control group with regards to NO levels. Our study results indicated that proanthocyanidin decreases lipid peroxidation, oxidative stress, neutrophil migration, and pulmonary damage.

Obstructive jaundice is associated with biliary infarctions and portal changes. Biliary infarction is related to the ductal damage due to increased biliary pressure, the direct effect of bile components on hepatocytes, and the indirect effects of bilirubin and bile acids in the blood (24). Edema, and neutrophil and lymphocyte infiltration can be observed in the first week

following obstruction. Portal inflammation and bile duct proliferation in the periportal area can also be seen (24). In our study, there was a statistically significant decrease in the treatment group in terms of liver micro-abscess and necrosis as compared to the control group ($p<0.05$). We determined that proanthocyanidins, which were selected due to their antioxidant properties, yielded a significant improvement on histopathologic disorders in obstructive jaundice. However, this improvement was not reflected in biochemical parameters and did not reach statistical significance. We also identified a significant improvement in the treatment group regarding NO levels, which are the best indicators of an antioxidant effect.

Chang and Ohara (25) detected cells resembling large mononuclear macrophages containing latex particles in the pulmonary capillaries of lung parenchyma in rats with obstructive jaundice. In these rats with obstructive jaundice, there was an increase in intravascular phagocytosis that led to pulmonary edema, which was reported to cause an inclination for sepsis and ARDS. We observed a significant decrease in pulmonary neutrophil leukocyte infiltration in the treatment group in comparison to the control group ($p<0.05$). Although the etiology of renal function disorders in obstructive jaundice is yet to be known, it has been suggested that cellular and extracellular hypovolemia, increase in oxygen free radicals, and decrease in antioxidant functions play a significant role (26, 27). While there was a decrease in the scope of renal tubule damage in the treatment group of our study, it was not statistically significant.

CONCLUSION

In conclusion, we have shown in our study that proanthocyanidin administration significantly decreased liver microabscess and necrosis as well as neutrophil migration in the lungs in obstructive jaundice. Furthermore, we have demonstrated that although it did not reach statistical significance, proanthocyanidin administration also reduced renal tubule damage. This improvement was also detected in NO levels. We concluded that proanthocyanidin is a natural antioxidant that is effective in reducing the scope of tissue damage caused by oxygen free radicals.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University (31.10.2012-2012/86).

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

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

Acknowledgements: The authors would like to thank Dr. Hakan Esen for this contributions.

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

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

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Turk J Surg 2017; 33: 69-75
DOI: 10.5152/turkjsurg.2017.3352

Analysis of risk factors affecting coagulopathy after donor hepatectomy in a newly established liver transplant center

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ABSTRACT

Objective: As might be expected, living donor liver surgery is associated with serious morbidity and mortality risks. Coagulopathy after donor hepatectomy is an important risk factor affecting morbidity. In this study, risk factors affecting the development of coagulopathy after donor hepatectomy was evaluated in a newly-established liver transplant center.

Material and Methods: A retrospective evaluation of 46 liver donors to whom hepatectomy was applied in Medipol Universty of School of Medicine Department of Organ Transplantation between April 2014 and July 2015 was made. Coagulopathy was defined as prothrombin time ≥15 sec. or platelet count <80000/mm^3 on postoperative day 3. Donors were separated into 2 groups as those with (n=24) and without (n=22) coagulopathy. Preoperative, intraoperative and postoperative factors acting on coagulopathy were analyzed.

Results: In the intergroup analysis, it was seen that remnant liver volume, remnant liver volume % and remnant liver volume to body weight ratio were factors associated with coagulopathy. The cut-off values for these 3 parameters were calculated as 773.5cm^3, 40.5% and 0.915 cm^3/kg, respectively. Only remnant liver volume % was determined as a risk factor for coagulopathy after donor hepatectomy on multiple logistic regression analysis.

Conclusion: The results of this study showed that the most important risk factors affecting coagulopathy after donor hepatectomy were the parameters associated with remnant liver volume.

Keywords: Donor hepatectomy, coagulopathy, remnant liver, risk factors

Cite this paper as:
Aktaş S, Sevmiş Ş, Şeker M, Korkut E, Karakayalı H. Analysis of risk factors affecting coagulopathy after donor hepatectomy in a newly established liver transplant center. Turk J Surg 2017; 33(2): 69-75

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Received: 08.09.2015
Accepted: 21.11.2015

Available online at
www.turkjsurg.com

INTRODUCTION

Liver transplant is a lifesaving treatment in end-stage acute and chronic liver failures, primary and secondary tumors of the liver, some metabolic diseases and post-traumatic massive liver injuries. Patients stay on the waiting lists for a long time due to the shortage in cadaveric donor organs, and may even die on the waiting list. In order to overcome this problem, living donor liver transplant (LDLT) has been commonly accepted worldwide. However, protecting the donor's health should always be the most important target in LDLT (1). Coagulopathy after major hepatic resections is an important risk factor that has an impact on postoperative morbidity (2, 3). This becomes more of an issue particularly in the planning of interventions such as epidural catheter removal, which may be risky in terms of bleeding. In this study, the risk factors affecting the development of coagulopathy after donor hepatectomy in a newly established liver transplant center were analyzed.

MATERIAL AND METHODS

Following the necessary legal preparations and inspections, Medipol Universty School of medicine Department of General Surgery was licensed to perform liver transplantations (license no 5064) by the Ministry of Health on 03.02.2014. The liver transplantation program was started on April 2014 and from that date to July 2015, 46 LDLT were performed in our center. Donors were accepted as temporarily coagulopathic when the prothrombin time was (PT)≥15 sec. or the platelet count was <80000/mm^3 on postoperative day 3 (4). According to these findings, donors were categorized as those with (n=24) and without (n=22) coagulopathy. This research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".

All relevant data during preoperative preparation, operation, postoperative follow-up and control periods of the donors were recorded systematically by the same physician. These data included donor age, gender, body mass index (BMI), biopsy findings (hydrops, sinusoidal dilatation, pigment accumulation, inflammatory infiltration, parenchymal focal necrosis, microvesicular steatosis, and macrovesicular steatosis), graft type, volumetric analysis of the liver calculated by multi-slice computerized tomography (CT) [total liver volume (TLV), functional liver volume (FLV), graft volume (GV), remnant liver volume

(RLV), percentage of remnant liver volume to total liver (RLV%), remnant liver to donor body weight ratio (RLBWR)], graft weight after hepatectomy (GW), peri-operative use of blood transfusion, fresh frozen plasma (FFP), amounts of crystalloid and colloid solutions, operation time, as well as intraoperative and postoperative complications. Philips Brillance ICT256-slice scanner system was used for visualization, assessment and quantification of the liver that is extracted from abdominal CT images specifically providing quantitative measurements of the liver volume, including blood supply and abnormalities within the liver. It also provides information of FLV by automatically removing vascular structure's volume from total liver volume. The RLV value was calculated on CT by extracting the volume of the liver lobe to be used as the graft from the total liver volume, and RLBWR was calculated as the ratio of RLV, as detected by CT, to body weight.

Donor Preparation

In our center, donor preparation starts with taking a detailed medical history and physical examination and progresses gradually to invasive tests. Mentally competent individuals between the ages of 18 and 65 years are accepted as donor candidates. According to the organ transplant laws of our country, the donor must be related to the recipient up to the 4th degree or his/her spouse, and if there is no such relationship then approval from the Ethics Committee of the Local Health Authority is required. There must be no compromise of the principles stating that there must be no pecuniary advantage in the relationship between the recipient and donor, and the donor must submit into the arrangement voluntarily without being under any sort of pressure.

All donors are evaluated by transplant surgeons, hepatologists, cardiologists, pulmonologists, and psychiatrists, female donors are also evaluated by gynecologists. In the first evaluation, all risks entailed in the donor surgery, operation and postoperative follow-up are explained in detail to the donor by the transplant surgeon. The parenchymal structure of the liver, the liver volume and vascular system, and the biliary system are analyzed thoroughly by ultrasound, CT and MRI, respectively. The donor is accepted when the RLV% is ≥35%, RLBWR is ≥0.6 and above, and the graft weight to recipient weight ratio (GBWR) is ≥0.8 and above. Regardless of the RLV%, a donor is not accepted if RLBWR is <0.6. The histopathologic appearance of the liver structure must be normal in liver biopsy.

Donor Surgical Procedure

Informed consent forms are received from all donors before the operation. Following anesthesia induction, 2 gr. of 2nd generation cephalosporin is used for prophylactic purposes. During the operation, the donors are monitored through electrocardiography, invasive blood pressure obtained from a catheter placed into the radial artery, central venous pressure obtained from the right internal jugular vein, and body temperature. Bilateral or right subcostal incisions extending from the midline to the xiphoid are performed for the operation. Vascular structures in the hilus are dissected following mobilization of the liver. Inferior hepatic veins with diameters >5 mm are dissected in a way to be anastomosed to the vena cava inferior, and veins with diameters <5 mm are transected with ligation. The biliary tract is defined with intraoperative cholangiography and cholecystectomy is performed. The demarcation line is determined by placing a temporary clamp on the hepatic artery and portal vein of the lobe to be removed in order to determine the right and left lobe resection lines. For the left lateral segment, this line is determined as the right side of the falciform ligament that is to remain on the graft. Dissection is performed so that the middle hepatic vein always remains on the left lobe. In right lobe grafts, veins draining segments 5-8 to the hepatic vein are dissected and preserved to be able to make a reconstruction if they are >5mm in diameter. Cavitron ultrasonic surgical aspirator (CUSA System 200 Macrodissector; Cavitron Surgical Systems, Stamford, CT, USA) is used for parenchymal dissection.

Following completion of parenchymal dissection, the biliary tract is checked again for leakage via the cystic duct. Then the hepatic artery, portal vein and hepatic vein of the graft to be received are clamped and cut and the graft is transported to the back-table for the preservation process. The remnant hepatic vein stump is closed with 4/0, and the remnant portal vein, hepatic artery and biliary tract are closed with 6/0 monofilament non-absorbable suture materials. The incision is closed in layers by placing a drainage catheter in the subhepatic region.

Postoperative Follow-up

Following extubation, the donor is transferred to the intensive care unit and monitored for 1 night. After recovering consciousness, the naso-gastric catheter is removed and oral liquid nutrition is started. The donor is mobilized after 6 hours. The urinary catheter is removed on the 1st postoperative day and the central venous catheter on the 3rd day on condition that the platelet count is 80000/mm^3 or above. Following 48 hours of controlled analgesia, oral analgesic agents are administered. Liver function tests are checked daily during the hospitalization period. The drainage tube is removed when the daily amount of serous drainage is <100 cc. Donors are generally discharged on the 4th-7th postoperative day. Follow-up examinations are made in 1 week after discharge, then at the 1st, 3rd, 6th and 12th months including Doppler USG and liver function tests.

Statistical Analysis

Statistical Package for the Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA) program was used for data analysis. The Shapiro-Wilk test was used for the conformity of the data to normal distribution, and the Leneve test was used for variance homogeneity. Independent-Samples T test was used with Bootstrap results and the Mann-Whitney U test was used with the Monte Carlo simulation method in the comparison of two independent groups. The Pearson Chi-Square and Fisher Exact tests were performed with the Monte Carlo Simulation method in the comparison of categorical data. Odds ratio was used for the determination of the most important risk factor among categorical significant risk factors. Logistic regression test was used to determine the cause and effect relationship of categorical response variable with explanatory variables in binary and multinominal categories. The relationship between the classification of groups separated by the cut-off value calculated according to variables and the real classification, sensitivity and specifity values were analyzed and stated by ROC (Receiver Operating Curve). Quantitative data were stated as mean±std.(standard deviation), range (Maximum-Minimum) and median range (Maximum-Minimum) values. Categorical data were stated as number (n) and percentage (%). The data

were analyzed at 95% confidence level and a value of $p<0.05$ was accepted as statistically significant.

RESULTS

Seventeen of the 46 donors were (37%) female, and 29 (63%) were male. The mean age of the donors was 35.24±7.5 years (25-55 years) in the group with coagulopathy, and 35±8.16 years (23-53 years) in the group without coagulopathy. Body mass index (BMI) was 27,23±4,01 (35,8-20) in the group with coagulopathy, and 27,12±4,11 (34,4-20) in the group without coagulopathy. The demographic data were similar in both groups. All patients with coagulopathy were diagnosed based on a PT value >15 sec. There were no donors with thrombocytopenia <80,000. There were no mortalities.

The 41 preoperative donor liver biopsies revealed 13 hydrops, 8 sinusoidal dilatation, 9 pigment deposition in hepatocytes, and 18 sparse focal necrosis. Microvesicular steatosis between 3-15% was observed in 13 donors and macrovesicular steatosis between 5-25% in 20 donors. Parenchymal structures were normal in all donors. No significant difference was seen between the groups in terms of all the parameters. The findings are summarized in Table 1.

Per-operative blood transfusions were performed on 21 donor operations. In 2 donor operations, significant bleeding occurred due to sliding of the vascular clamp on the vena cava securing the hepatic vein stump. No significant difference was seen between the groups in terms of intraoperative blood transfusion requirements, crystalloid and colloid fluid amounts given, operation times and intraoperative complications (Table 2).

When volumetric analysis results were examined, it was seen that there was no significant difference between the groups with regards to TLV, FLV, GV and graft type. GW results were also similar. However, the parameters of RLV [602 cm^3, (413-1450 cm^3) versus 670 cm^3, (503-1469 cm^3), p=0.046], RLV% [39%, (35-80%) versus 42.5%, (37-85%), p=0.004], and RLBWR [0.79%/kg, (0.59-1.64%/kg) versus 0.915 (0.67-1.8%/kg),

Table 1. Histopathologic findings of donor liver biopsies with or without coagulopathy

	No coagulopathy (n=22)	Coagulopathy (n=24)	p
Sex (female/male)	10 (45.5)/12 (54.5)	7(29.2)/17 (70.8)	0.361
Age, years	35.00±8.16 (53-23)	35.25±7.50 (55-25)	0.914
BMI, kg/m^2	27.12±4.11 (34.4-20)	27.23±4.01 (35.8-20)	0.942
Hemoglobin, g/dL	14.45±1.89 (18-9.9)	14.35±2.00 (19.9-10.2)	0.859
White Blood cell, 10e3/uL	7.79±1.49 (10.8-5.4)	7.28±2.01 (11.9-4.6)	0.334
Platelet, 10e3/uL	251.18±68.18 (378-129)	232.79±61.04 (405-130)	0.340
PT, s	13.11±0.68 (14.6-12.3)	13.44±0.77 (14.9-12.2)	0.123
INR	1.03±0.09 (1.2-0.9)	1.09±0.09 (1.25-0.89)	0.039
AST, U/L	17 (44-10.7)	16 (34-11)	0.683
ALT, U/L	17.5 (54-8.6)	16 (60-6.9)	0.891
Albumin	4.56±0.38 (5.3-3.5)	4.47±0.26 (5-4.1)	0.316
Total Bilirubin mg/dL	0.415 (3.2-0.2)	0.5 (1.4-0.2)	0.688
Direct Bilirubin mg/dL	0.2 (0.9-0.1)	0.2 (0.4-0.1)	0.710

Fisher Exact Test (Monte Carlo); Independent T Test (Bootstrap); Mann-Whitney U Test (Monte Carlo); Mean±Sd (standard deviation); Range (maximum-minimum); Median Range (maximum-minimum); n (%)
BMI: Body Mass Index; PT: prothrombin time; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Table 2. Intraoperative characteristics of donors with or without coagulopathy

	No coagulopathy (n=22)	Coagulopathy (n=24)	p
Biopsy (no/yes)	4 (18.2)/18 (81.8)	1 (4.2)/23 (95.8)	0.178
Hidrops (no/yes)	15 (78.9)/4 (21.1)	15 (62.5)/9 (37.5)	0.324
Sinusoidal dilatation (no/yes)	15 (83.3)/3 (16.7)	17 (77.3)/5 (22.7)	0.709
Collection of pigment (no/yes)	13 (72.2)/5 (27.8)	18 (81.8)/4 (18.2)	0.705
Inflammatory infiltration (no/yes)	13 (72.2)/5 (27.8)	10 (43.5)/13 (56.5)	0.112
Focal Necrosis (no/yes)	11 (61.1)/7 (38.9)	11 (50)/11 (50)	0.537
Microvesicular steatosis (no/yes)	11 (61.1)/7 (38.9)	16 (72.7)/6 (27.3)	0.509
Macrovesicular steatosis (no/yes)	9(50) / 9(50)	11 (50)/11 (50)	1

Fisher Exact Test (Monte Carlo)
n (%)

Table 3. Multi-slice computed tomography (CT) findings of donors with or without coagulopathy

	No coagulopathy (n=22)	Coagulopathy (n=24)	p
TLV	1.616.95±201.10 (1952-1256)	1.582.29±206.55 (2115-1190)	0.553
FLV	1.561.05±194.59 (1883-1217)	1.524.83±199.73 (2050-1149)	0.523
GV	868 (1100-236)	918.5 (1278-258)	0.508
Type of graft (left/right)	5 / 17	2/ 22	0.234
GW	920 (1050-220)	935 (1150-320)	0.324
RLV	670 (1469-503)	602.5 (1450-413)	0.046
RLV%	42.5 (85-37)	39 (80-35)	0.004
RLBWR	0.915 (1.8-0.67)	0.79 (1.64-0.59)	0.034

Fisher exact Test (Monte Carlo); Independent T Test (Bootstrap); Mann-Whitney U Test (Monte Carlo); Mean±Sd (standard deviation); Range (maximum-minimum); Median Range (maximum-minimum); n (%)
TLV: total liver volume; FLV: functional liver volume; GV: graft volume; GW: graft weight calculated intraoperatively, RLV: remnant liver volume; RLBWR: remnant liver body weight ratio

Table 4. Analysis of factors predict coagulopathy of donor's using Roc curve with or without coagulopathy

	No coagulopathy (n=22)	Coagulopathy (n=24)	p
TLV	1.616.95±201.10 (1952-1256)	1.582.29±206.55 (2115-1190)	0.553
FRV	1.561.05±194.59 (1883-1217)	1.524.83±199.73 (2050-1149)	0.523
GV	868 (1100-236)	918.5 (1278-258)	0.508
Type of graft (Left/Right)	5 (22.7)/17 (77.3)	2 (8.3)/22 (9.7)	0.234
GW	920 (1050-220)	935 (1150-320)	0.324
RLV	670 (1469-503)	602.5 (1450-413)	0.046
RLV%	42.5 (85-37)	39 (80-35)	0.004
RLBWR	0.915 (1.8-0.67)	0.79 (1.64-0.59)	0.034

Fisher exact Test (Monte Carlo); Independent T Test(Bootstrap); Mann-Whitney U Test (Monte Carlo); Mean±Sd (standard deviation); Range (maximum-minimum); Median Range (maximum-minimum); n (%)
TLV: total liver volume; FRV: functional liver volume; GV: graft volume; GW: graft weight which calculate intraoperatively; RLV: remnant liver volume: RLBWR: remnant liver body weight ratio

p=0.034] were significantly lower in the group with coagulopathy. The findings are summarized in Table 3 and Figure 1a-c.

In the intergroup analyses, the ROC curve and cut-off values were calculated for RLV, RLV% and RLBWR parameters, which were determined to have an effect on coagulopathy. In these analyses, the cut-off values were calculated as 773.5 cm^3, 40.5% and 0.915%/kg, respectively, for RLV, RLV% and RLBWR. All three values were statistically significant. The analysis results are summarized in Table 4 and Figure 2.

Remnant liver volume, RLV% and RLBWR values, for which significant results were found in the statistical analyses performed based on the cut-off values, were analyzed again with the multiple logistic regression model. In this analysis, as summarized in Table 5, RLV% of <40.5% was seen as a statistically significant risk factor for the development of coagulopathy [(p=0.01, AUC±Se:0.745±0.073, Odds Ratio (95%C.I):0.188 (0.053-0.664)].

DISCUSSION

Liver transplant is the only curative treatment for end-stage liver failure, acute liver failure, some metabolic diseases and for some tumors of the liver. Increasing number of liver transplants are being performed using partial grafts obtained from living donors due to the shortage of cadaveric donor organs in developing countries, such as Turkey. Living-donor liver transplantation has the advantages of shortening the waiting time, extending life expectancy and that it can be performed under elective conditions (5). LDLT requires a donor who has been tested and confirmed to be sufficiently healthy to be exposed to an operation with serious morbidity and mortality risks. Therefore, the main duty and responsibility of organ transplant surgeons are to protect the donor's health and to minimize any risks associated with the operation. Despite developments in surgical techniques and experiences, a complication rate of approximately 38% and a mortality rate of 0.2% has been reported. Fortunately, almost all donors return to their normal lives at 3-6 months postoperatively (6-8). There is a higher rate of complications and mortality in right lobe donors with a long-term negative effect on quality of life. The only reason of the higher mortality and morbidity rate in right lobe donors is the greater liver volume to be removed (8, 9). In the current study, 39 donors underwent right hepatectomy while 7 underwent left lobe or left lateral segment resection. Of the donors with coagulopathy, right lobectomy was applied to 22 cases and left lobe or left lateral segment hepatectomy to 2.

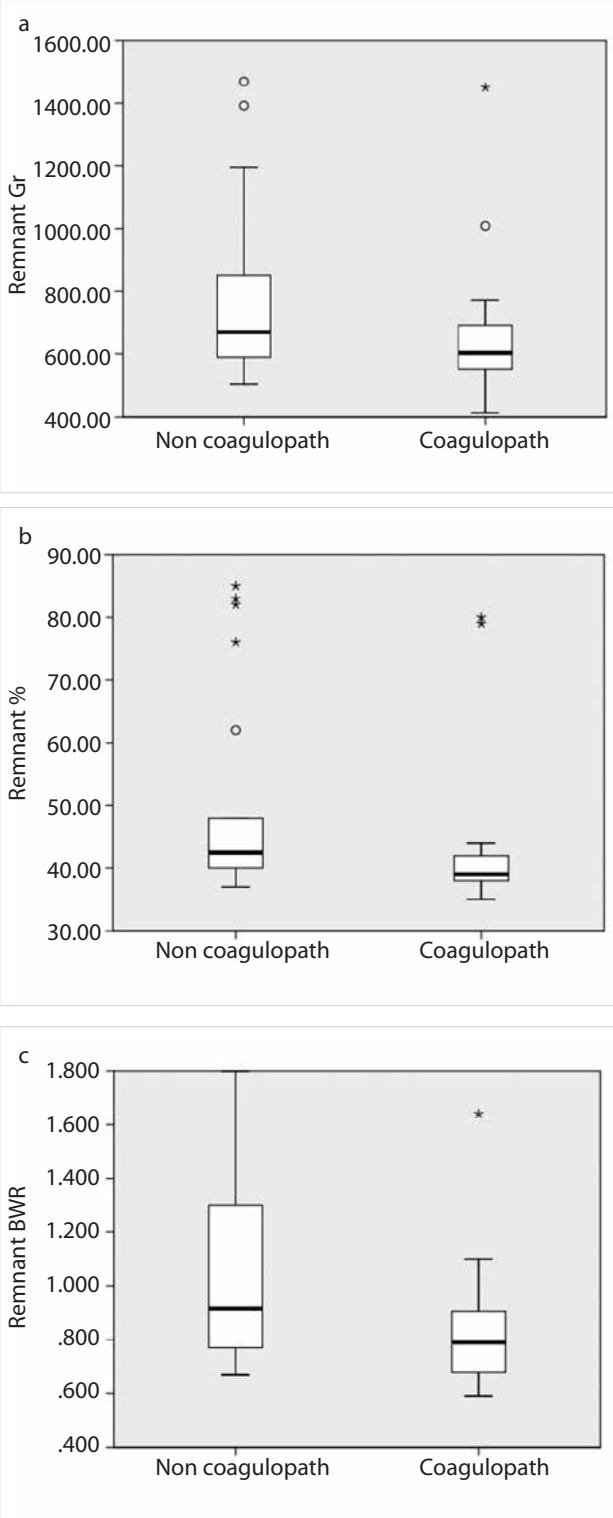

Figure 1. a-c. (a) Analysis of factors predicting coagulopathy in donor's remnant liver volume (RLV), (b) Analysis of factors predicting coagulopathy in donor's % remnant liver volume (%RLV), (c) Analysis of factors predicting coagulopathy in donor'sremnant volume to body weight ratio (RLBWR)

Major hepatic resection leads to a reduction in liver tissue that synthesizes coagulation factors and accordingly to the development of coagulopathy (3, 10). Temporary coagulopathy has been reported after resections performed for LDLT and liver tumors (4, 10-12). In these studies; hemorrhage, transfusion, temporary cessation of liver blood flow, fibrinolysis, high BMI,

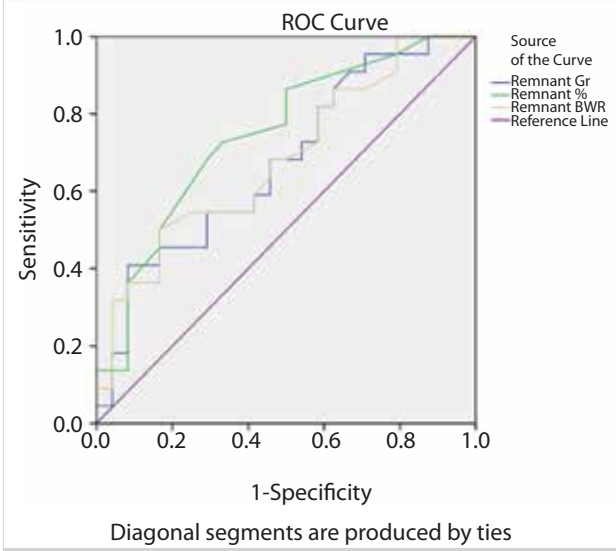

Figure 2. ROC curve analysis

and decrease of synthetic activity have been reported as factors affecting coagulopathy. The Pringle's maneuver used for reducing hemorrhage has been reported as an independent risk factor that affects coagulopathy (13). In the current series, there was no bleeding that required temporary occlusion of liver blood flow. RLV% was found to be a risk factor affecting coagulopathy development.

Coagulopathy is often accepted as a situation that jeopardizes donor safety, although it is not a factor that extends length of hospital stay in donors. In these patients who undergo major surgery, perioperative monitoring is obtained by central, epidural and arterial catheters, which carry the risk of bleeding in a coagulopathic environment when they are removed. Karna et al. (3) suggested that the INR value should be <1.5 for the epidural catheter to be removed safely, and therefore this catheter should not be removed during the first 4 days after hepatectomy. In another study, it was reported that invasive catheters could be removed safely in cases where the platelet count is 100 000/mm^3 (14). In our center, epidural anesthesia is not used. The central venous catheter used for monitoring is generally removed on the 3rd postoperative day, when the platelet count is ≥80000/mm^3. No complications were recorded associated with the removal of the catheters.

Due to the higher volume of liver removed after right lobe donor hepatectomy, there is a higher risk of coagulopathy development as compared to left lobe procedures. Remnant liver volume measured with CT is generally stated as %. In previous studies, it has been shown that hepatectomy could be implemented safely when the RLV is >30%, and complications have been reported to significantly increase in donors with a RLV of <30%. The same studies have also reported that the rate of coagulopathy was higher in donors with lower RLV percentages (3, 15, 16). Fan et al. (17) reported that the minimum remnant volume should be ≥ 30% for donors. In the current series, RLV <40.5% was determined as an independent risk factor on the development of coagulopathy. In line with this data, although it has been stated that hepatectomy performed with RLV >30% is safe, it should be kept in mind that a completely healthy individual underwent a major operation.

Table 5. Analysis of factors predict coagulopathy of donor's using Roc curve with or without coagulopathy

	Cut-offs	No Coagulopathy (n=22)	Coagulopathy (n=24)	Odds Ratio (95%C.I)	AUC±Se	p
INR	<1.035 >1.035	12 (54.5)** 10 (45.5)	6 (25) 18 (75)*	3.6 (1.033-12.542)	0.663±0.080	0.059
RLV	<773.5 >773.5	9 (40.9)** 13 (59.1)	2 (8.3) 22 (91.7)*	7.615 (1.421-40.803)	0.673±0.080	0.004
%RLV	>40.5 <40.5	16 (72.7)** 6 (27.3)	8 (33.3) 16 (66.7)*	5.33 (1.505-18.899)	0.745±0.073	0.004
RLBWR	>0.915 <0.915	11 (50)** 11 (50)	4 (16.7) 20 (83.3)*	5.0 (1.283-19.490)	0.683±0.079	0.034

Roc Curve Analysis (Youden index J - Honley&Mc Nell)
*Sensitivity
**Specificity
[a]significant odds ratio
AUC: area under the ROC curve; Se: standard error; C.I: confidence interval; RLV: remnant liver volume; RLBWR: remnant liver body weight ratio

In a series of 74 cases of major liver resections for liver disease, Truant et al. (18) reported that hepatectomy could safely be performed when RLV% is >20% and RLBWR is >0.5, and that liver failure and thus mortality rates were higher in cases where the values were below these levels. In another study, the cut-off value for RLBWR was stated as 0.4 in patients with liver disease (19). In a study of 83 cases, Radtke et al. (20) reported that temporary small-for-size syndrome developed in 3 living donors. The RLBWR values of those 3 patients were given as 0.6 and 0.5. In another study, it was reported that morbidity was significantly higher when RLV% was <30% and RLBWR <0.6 (21). In our center, it is accepted that RLBWR should be ≥0.6 for LDLT. In this study, the cut-off value for RLBWR was determined as 0.915, there was determined to be a possibility of estimating coagulopathy development with 83% sensitivity. Although an extensive resection is acceptable in patients with liver disease, even with poor results, a living liver donor who is known to be completely healthy should never be jeopardized.

CONCLUSION

The most important risk factors affecting coagulopathy after donor hepatectomy are remnant liver volume and its associated parameters. It must be taken into consideration that coagulopathy is an important factor that affects donor survival and morbidity. Donor selections must be made more liberally.

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

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

Peer-review: Externally peer-reviewed.

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

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

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

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Turk J Surg 2017; 33: 76-79
DOI: 10.5152/turkjsurg.2017.3392

Can red cell distribution width be used as a predictor of acute cholecystitis?

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ABSTRACT

Objective: Acute cholecystitis is a common disease requiring accurate markers for diagnosis and proper treatment. The aim of this study was to investigate the role of red cell distribution width (RDW) in acute cholecystitis.

Material and Methods: 299 were included in the study. The subjects were divided into 2 groups; group 1 (n: 46) acute cholecystitis group and group 2 (n: 253) chronic cholecystitis group. The patients were compared with respect to demographic characteristics, white blood cell count, C-reactive protein, and red cell distribution width.

Results: A statistically significant difference was observed between groups with respect to gender, white blood cell count, C-reactive protein, and red cell distribution width level ($p<0.05$). The mean red cell distribution width level of group 1 and 2 was 14.19±2.02% and 15.03±2.51%, respectively.

Conclusion: Red cell distribution width level can be used as a predictor of acute cholecystitis. Multicenter prospective studies should be performed to elucidate the exact role of RDW level in acute cholecystitis.

Keywords: Acute cholecystitis, C-Reactive protein, white blood cell count, red cell distribution width

INTRODUCTION

Acute cholecystitis (AC) is among the most common reasons of acute abdomen presenting to emergency departments and is commonly related to the obstruction of the cystic duct mainly with gallstones. The prevalence of cholelithiasis is reported as 10-15%, and approximately 35% of these patients develop complications or recurrent symptoms in their lifetime (1, 2). Although more than 70% of patients with acute cholecystitis respond to medical treatment within the first 24-48 hours, laparoscopic cholecystectomy (LC) is the definitive treatment of symptomatic cholelithiasis and its complications. Early LC has been reported to have lower complication rates than open cholecystectomy (OC) (3). Although the timing of LC remains controversial, early LC is recommended for reduction of complication rate and length of hospital stay (4-7). Early diagnosis of acute cholecystitis is necessary for the decision of surgery.

The diagnosis of AC is based on severe abdominal pain at the right upper abdominal quadrant and localized tenderness (with or without a positive Murphy's sign) together with vomiting, fever and leukocytosis (8). Ultrasound findings support acute cholecystitis (9, 10). Diagnosis of AC can also be confirmed by pathology findings.

The laboratory tests can be easily performed and facilitate AC diagnosis, which include; complete blood count (CBC), C-Reactive protein (CRP) and liver function tests. CBC includes leukocyte, erythrocyte and thrombocyte counts and also morphological features such as red cell distribution width (RDW). Red cell distribution width level has been reported to be a predictor of diseases such as coronary artery disease, inflammatory bowel disease, celiac disease and pulmonary embolism, and has been reported to be valuable in diagnosis of diseases such as acute pancreatitis, bacteremia, sepsis, and septic shock (11, 15-17). However, the role of RDW in diagnosis of AC remains unclear. The aim of this study was to investigate the role of RDW in AC.

MATERIAL AND METHODS

All patients who underwent laparoscopic cholecystectomy between January 2013 and July 2014 in Başkent University Adana Application and Research Center General Surgery Department were included in the study. Patients were divided into two groups according to their final pathology reports. Group-1 consisted of patients with acute cholecystitis while group-2 consisted of patients with chronic cholecystitis (CC). Data was collected retrospectively. Demographic data such as age and sex, physical findings (Murphy's sign), white blood cell count, RDW level, CRP level, ultrasound findings, pathology report, ASA (American Society of Anesthesiologists) score and complications were recorded. Exclusion criteria

Cite this paper as:
Arer İM, Yabanoğlu H, Çalışkan K. Can red cell distribution width be used as a predictor of acute cholecystitis?. Turk J Surg 2017; 33(2): 76-79

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Received: 23.09.2015
Accepted: 01.12.2015

Available online at
www.turkjsurg.com

included cholangitis, choledocholithiasis, acute pancreatitis, malignancy, and a history of percutaneous or endoscopic biliary drainage prior to surgery.

This study was approved by Başkent University Institutional Review Board (Project No: KA14/258) and supported by Başkent University Research Fund. Informed consent was not taken because of the retrospective design of this study.

Laboratory Tests

Leukocyte counts were obtained by an electronic cell counter (Advia 2120i; Hematology System with Autoslide, Siemens, Erlangen, Germany). Serum CRP levels were measured by spectrophotometric methods (Cobas Integra 800; Roche, Mannheim, Germany). The normal range of RDW level in our laboratory was 11.3-15.2%, that of leukocyte count was 4 and 11.5x10^3/μL, and that of CRP level was 0-6 mg/L.

Statistical Analysis

Statistical Package for the Social Sciences software package was used for statistical analysis (version 17.0, SPSS Inc.; Chicago, IL, USA). If continuous variables were normal, they were presented as mean±standard deviation (p>0.05 in Kolmogorov-Smirnov test or Shapira-Wilk (n<30)), and if the continuous variables were not normal, they were presented as median values. Comparisons between groups were applied using one-way Student T test and One Way ANOVA for normally distributed data. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Group-1 consisted of 46 patients while there were 253 patients in group-2, yielding a total of 299 subjects (206 female, 93 male). Within the group of 299 patients, 144 had positive physical findings and Murphy's sign (48.2%). There was no significant difference between groups according to age and ASA-score (p>0.05). A significant difference was determined between group-1 and 2 in terms of gender (p=0.001) (Table 1). Ultrasound findings revealed acute cholecystitis in 37 (12.4%), and chronic cholecystitis in 152 (50.8%) patients. In 110 (36.8%) patients, ultrasound was performed in another clinic. Detailed radiologic evaluation (e.g. Computed Tomography or Magnetic Resonance Cholongiopancreatography) was performed in 39 patients. Ten (3.3%) of these 39 patients were accepted as acute cholecystitis based on the findings of detailed radiologic evaluation (Table 2). The ASA-score of patients are listed in Table 3. The mean WBC count was 13.3±5.5 x10^3/μL and 8.8±2.8 x10^3/μL for group 1 and 2, respectively. The WBC count was significantly high in the AC group (p=0.001). Mean CRP level was 79.94±93.06 mg/L in the AC group and 32.94±51.27 mg/L in the CC group. The CRP level in the AC group was significantly high as compared with the CC group (p=0.030). However, the CRP level was recorded in only 17 of 46 AC and 30 of 253 CC patients, which is the main limitation of our study regarding CRP level comparison. The mean RDW level was 14.19±2.02% in the AC group and 15.03±2.51% in the CC group. The RDW level was significantly low in the AC group (p=0.034). Receiver operating characteristic (ROC) curve analysis showed the best cut-off value for RDW level in the diagnosis of AC as 14.15% with a sensitivity of 64.8% and a specificity of 56.5% (area under curve [AUC]: 0.611, p=0.017; Figure 1). Receiver operating characteristic curve analysis identified the best cut-off value

Table 1. Comparison of the demographic features and White blood cell count, CRP, and RDW levels of the subjects in acute and chronic cholecystitis groups

	Acute cholecystitis (n=46)	Chronic cholecystitis (n=253)	p
Male/Female	24/22	69/184	0.001
Age (years)*	49.15±14.2	50.95±14.56	0.441
WBC (x10^3/μL)*	13.3±5.5	8.8±2.8	0.001
CRP (mg/L)*	79.94±93.06	32.94±51.27	0.030
RDW (%)*	14.19±2.02	15.03±2.5	0.034

*Values are mean±standard deviation.
CRP: C-reactive protein; RDW: red cell distribution width; WBC: white blood cell count

Table 2. Detailed radiologic evaluation

	Frequency (n)	Percent (%)
Acute cholecystitis (CT)	8	2
Acute cholecystitis (MRCP)	1	0.3
Gangrenous cholecystitis (CT)	1	0.3
Normal (CT)	4	1.3
Cholelithiasis (MRCP)	25	8.4
None	260	87
Total	299	100

CT: computed tomography, MRCP: magnetic resonance cholangiopancreatography

Table 3. ASA score of patients

ASA score	Frequency	Percent
1	44	14.7
2	175	58.5
3	79	26.4
4	1	0.3
Total	299	100

ASA: American Society of Anesthesiologists

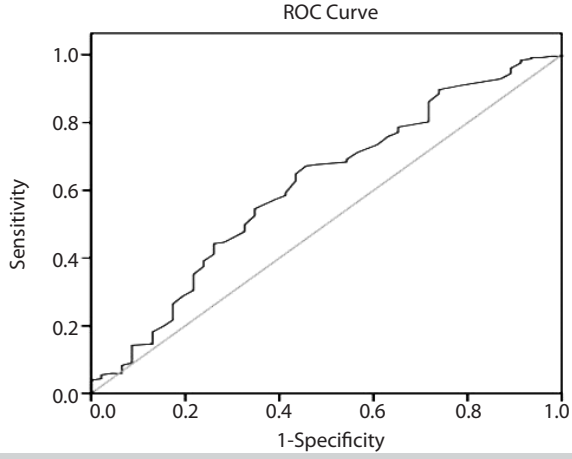

Figure 1. Receiver operating characteristic (ROC) curve of red cell distribution width (RDW)

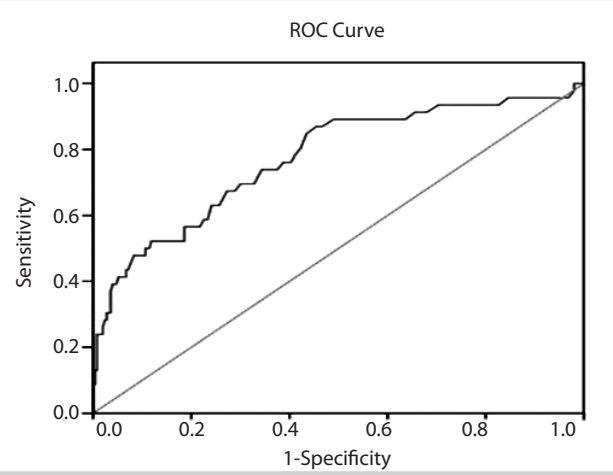

Figure 2. Receiver operating characteristic (ROC) curve of white blood cell (WBC) count

for WBC count in the diagnosis of AC as 9.9 x10^3/μL with a sensitivity of 69.6% and a specificity of 70% (area under curve [AUC]: 0.773, p=0.0001; Figure 2). No complication was observed in both groups.

DISCUSSION

Acute cholecystitis (AC) is among the most common reasons of acute abdomen presenting to emergency departments. Early diagnosis is essential for the decision of cholecystectomy timing. Early cholecystectomy, especially within 72 hours of admission, is recommended in order to decrease the complication rate and length of hospital stay (4-7). In a large randomized trial, Gutt et al. (18) showed that laparoscopic cholecystectomy was superior to conservative approach in terms of morbidity and cost. Therefore, early diagnosis and surgical decision making are crucial steps in the management of AC.

Elevated white blood cell count and CRP levels are common laboratory tests used in the diagnosis of AC. In our study, WBC count was found to be significantly high in the AC group, in parallel with previous reports (7, 19). The mean WBC count in our study was 13.3±5.5 x10^3/μL. Wevers et al. (19) determined the mean WBC count as 12.6-13.1 x10^3/μL. This elevated value may be due to high patient population presenting with severe cholecystitis. Although they did not report the exact WBC count in their series, Oymaci et al. (7) defined leukocytosis as WBC count higher than 10 x10^3/μL and 70-73% of their patients had leukocytosis. Nikfarjam et al. (20) found median WBC count as 11.7 x10^3/μL. In our study, the median WBC count was 12.5 x10^3/μL that is higher than that reported in the literature.

C-reactive protein level was also found to be elevated in AC, especially to very high values when gangrenous cholecystitis is present and Crp level is alsocorrelated with conversion to open cholecystectomy (19-21). In our study, the mean CRP level was 79.94±93.06 mg/L in the AC group and was statistically significant as compared to the CC group (p=0.030).

We aimed to seek another laboratory test that may aid in differentiating AC from CC. Red cell distribution width is a marker used in the differential diagnosis of microcytic anemia, thalassemia and hemoglobinopathies, while it can also reflect an inflammation (12, 22). Increased RDW levels are detected in cases of red blood cell production or degradation impairment (12). Higher RDW levels were found to be associated with worse clinical outcomes in patients with heart failure, coronary artery disease, pulmonary hypertension, diabetes mellitus, and stroke (13-15, 22-24). Pro-inflammatory cytokines of sepsis influence the half-life of circulating erythrocytes, damage their membranes and suppress maturation, lead to introduction of larger and newer reticulocytes to systemic circulation thus increasing the RDW. In addition, high oxidative stress can also reduce erythrocyte lifetime and increase the release of premature red blood cells into the blood stream. Sadaka et al. (25) demonstrated RDW to be associated with mortality and morbidity on the first day of septic shock. Meynaar et al. (26) showed that RDW level on Intensive Care Unit (ICU) admission was an independent predictor of mortality, but the mechanism of this association needs to be further investigated. Senol et al. (17) demonstrated that increased RDW-level on admission is an independent risk factor of mortality in patients with acute pancreatitis. Jo et al. (16) observed that RDW is associated with early mortality in severe sepsis and septic shock. the median RDW-level was similar in the non-survivor groups of both studies (16, 17). Increased RDW-level has been shown to be associated with elevated CRP, erythrocyte sedimentation rate, and interleukin-6 levels (22, 25, 27). Narci et al. (28) determined decreased RDW level in patients with acute appendicitis with a sensitivity and specificity of 47% and 67%, respectively. However, the difference was so slight that it was concluded that RDW could not be used in diagnostic testing. Yao et al. (29) also found a significant association between RDW and mortality in acute pancreatitis, and the sensitivity and specificity of RDW level to predict mortality were identified as 75% and 89.8%, respectively. In the literature, there are several studies evaluating the association between RDW level and acute pancreatitis or acute appendicitis, but no study was found to evaluate acute cholecystitis. Our study was designed to assess the correlation of acute cholecystitis and RDW level. We observed significant difference between RDW level and acute cholecystitis and mean RDW level was lower in AC group but still in normal range. We determined the sensitivity and specificity of RDW level in the diagnosis of AC as 64.8% and 56.5%, respectively.

We want to emphasize that mean RDW level in the CC group was 15.03%, which is close to the upper range of normal RDW level. The retrospective design of our study is one of its limitations. In addition, our control group consisted of patients with chronic cholecystitis, comparison versus the normal population without any inflammatory process may have yielded better results.

CONCLUSION

Elevated white blood cell count and C-reactive protein levels are predictors of acute cholecystitis. Red cell distribution width level has a similar significant role, which can be used as a predictor of acute cholecystitis. Multicenter prospective are required on this issue to further elucidate the role of RDW level in acute cholecystitis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Başkent University Institutional Review Board (Project No: KA14/258).

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

Peer-review: Externally peer-reviewed.

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

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

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

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Turk J Surg 2017; 33: 80-86
DOI: 10.5152/UCD.2016.3305

Outcomes of early cholecystectomy (within 7 days of admission) for acute cholecystitis according to diagnosis and severity grading by Tokyo 2013 Guideline

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ABSTRACT

Objective: The timing of early cholecystectomy in acute cholecystitis is still controversial, and data regarding the use of Tokyo 2013 guideline for diagnosis and severity grading in Acute Cholecystitis is limited. The aim of this study was to evaluate the clinical and pathologic outcomes of early cholecystectomy after 72 hr and within seven days of index admission according to Tokyo 2013 guideline for diagnosis and severity grading of Acute cholecystitis (in patients with Acute cholecystitis.

Material and Methods: Medical charts of 172 patients who underwent early cholecystectomy after 72 hr and within 7 days of index admission with a diagnosis of Acute cholecystitis between Aug 2009 and Apr 2014 were retrospectively analyzed. Patients were classified according Tokyo 2013 guideline criteria.

Results: The median age of the study group was 52 yr. The rates of open and laparoscopic cholecystectomies was 53.5% and 33.1%, respectively. Conversion to open cholecystectomy was performed in 19 patients (13.4 %). The median length of hospital stay was 7 days. Eighty-four patients (59.2%) met the criteria for a definite diagnosis of Acute cholecystitis according to Tokyo 2013 guideline. Longer postoperative and total length of hospital stay was determined in patients with a definite diagnosis.

Conclusion: Increased severity grading is correlated with longer pre- and post-operative hospital stay. Early cholecystectomy in Acute cholecystitis performed by experienced surgeons after 72 hr of admission and within 7 days maybe a feasible and safe procedure.

Keywords: Acute cholecystitis, diagnosis, early cholecystectomy, Tokyo 2013 guideline, severity grading

Cite this paper as: Sert İ, İpekci F, Engin Ö, Karaoğlan M, Çetindağ Ö. Outcomes of early cholecystectomy (within 7 days of admission) for acute cholecystitis according to diagnosis and severity grading by Tokyo 2013 Guideline. Turk J Surg 2017; 33(2): 80-86

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

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Received: 30.07.2015
Accepted: 01.11.2015

Available online at
www.turkjsurg.com

INTRODUCTION

Gallstones represent a common health problem (6.5-15%) in the Western population (1, 2). Approximately 1-4% of these patients develop complications (mainly acute cholecystitis (AC)) related to the gallbladder stone every year (3). Although the safety and feasibility of early cholecystectomy in the treatment of acute cholecystitis have been demonstrated, there is still no current consensus on the timing of early cholecystectomy (4-9). According to Tokyo 2013 guidelines (TG 13) for diagnosis and severity grading of acute cholecystitis (TG 13), early laparoscopic cholecystectomy for acute cholecystitis should be performed within 72 hrs. from the onset of symptoms (10). In daily practice, patients with acute cholecystitis who present 72hr later than the onset of symptoms are generally referred to interval cholecystectomy after medical treatment.

Interval cholecystectomy has some disadvantages including the need for emergency surgery due to failure of medical treatment, re-hospitalization due to symptom recurrence, a difficult and unsafe interval cholecystectomy because of fibrosis, an increase in health-expenditure due to re-hospitalization, and the possibility of being lost to follow-up (11). Owing to these above mentioned factors, the definition of 72 hr for early laparoscopic cholecystectomy has recently been changed. The early period is now defined as 24 h-7 days, based on multicenter randomized controlled studies (5, 12).

Although, the timing of early laparoscopic cholecystectomy is still controversial, early laparoscopic cholecystectomy gains acceptance day by day. Although several guidelines suggest ELC in acute cholecystitis (10-13), the rate of early cholecystectomy still remains low i.e. 15-40% (14-16).

A standard approach on the definition and severity assessment of acute cholecystitis is not present. TG 13 describes the diagnosis, severity grading and treatment strategies for acute cholecystitis. By the help of TG 13, the diagnostic sensitivity of acute cholecystitis increased while the rate of false positivity decreased. Moreover, the criteria defined for severity assessment are adopted to daily clinical practice (17).

The aim of the present study was to evaluate the clinical and pathologic outcomes of early cholecystectomy after 72 hr and within seven days of index admission in patients with acute cholecystitis according to TG 13 for the diagnosis and severity grading of acute cholecystitis.

MATERIAL AND METHODS

Medical charts of 172 patients who underwent early cholecystectomy after 72 hr and within 7 days of index admission with a diagnosis of acute cholecystitis between Aug 2009 and Apr 2014 were retrospectively analyzed. A total of 142 patients that met the inclusion criteria were enrolled. Patient demographic data (age, gender, comorbidities, etc.), time to operation, antibiotic therapy, ASA score, surgical procedure, postoperative complications, length of hospital stay were documented. This study has been approved by the local ethic committee of Tepecik Training and Research hospital. Patient informed consent was not obtained due to retrospective nature of the study.

Patients under 18 years old, those with acute pancreatitis (n: 5), acute cholangitis (n: 1), acalculous cholecystitis, or choledocholithiasis (n: 7), those who have been conservatively treated (n: 5), not underwent cholecystectomy within 7 days of index admission (n: 8), and with a missing final pathology report (n: 4) were excluded from the study. All patients in the study underwent early cholecystectomy between 3-7 days of index admission.

Diagnosis of acute cholecystitis was based on patients local examination (Murphy's sign, pain, tenderness or mass in right upper quadrant), systemic (fever, high CRP levels or abnormal white blood cell count), and imaging (gallbladder stones, thickened gallbladder wall (>4mm), pericholecystic fluid, sonographic Murphy's sign) findings according to TG 13 (18). Patients were classified as those with a suspected diagnosis (having positive local and systemic findings) or with a definite diagnosis (having positive local, systemic and imaging findings) groups. Patients were then clinically graded for severity as mild, moderate or severe according to severity grading of TG 13 (18). According to final histology reports, patients with acute cholecystitis were also divided into four groups as acute, phlegmonous, gangrenous, and chronic cholecystitis.

Surgical procedures were simply categorized as open, laparoscopic and conversion from laparoscopic to open cholecystectomy. Laparoscopic cholecystectomy was performed with standard 4 trocar operative technique. Planned open cholecystectomy was performed with a right subcostal incision. In case of presence of distended gallbladder, it was decompressed by using a needle. In the presence of a phlegmon, blunt dissection was performed and the cleavage composed by omentum and surrounding tissues was followed. Dissection was performed by using monopolar cautery or sealing devices. Cholecystectomy was not performed without identification of all structures within Callot's triangle. All operations were performed by experienced surgeons. A standard objective criterion was not used to convert from laparoscopy to open cholecystectomy. Decision of conversion to open cholecystectomy was based on surgeon preference, history of previous abdominal surgery, clinical and laboratory findings, and disease severity. A subhepatic drain was almost always inserted. The drain was generally removed at postoperative day 1. None of the patients had percutaneous cholecystectomy or partial cholecystectomy. The timing of the operation was determined according to clinical and laboratory response to medical treatment, and feasibility of the operating theater. If needed, magnetic resonance cholangiography was obtained. Intraoperative cholangiography was not performed.

All patients received intravenous antibiotic treatment on admission. Antibiotherapy was continued for 24 hrs. after surgery. Oral intake was resumed after one or two days according to clinical and laboratory findings. During this period, parenteral fluid support was ensured. Perioperative local and systemic complications were recorded.

Statistical Analysis

All statistical analysis was performed with the Statistical Package for the Social Sciences for Windows, version 15.0 software program (SPSS Inc.; Chicago, IL, USA). Continuous variables are presented as means±SD, and categorical variables as frequencies and percentages. Continuous variables were compared using Student-t test or Wilcoxon test when appropriate. Chi-square or fisher exact test was performed for comparison of differences in categorical variables. $p<0.05$ was considered statistically significant. Risk factors for conversion and factors related to pre-operative, post-operative and total length of hospital stay were evaluated in a univariate model, and statistically significant parameters were then evaluated in a multivariate analysis to determine the independent factors. Odds ratio and 95% confidence intervals (CI 95%) were calculated using a logistic regression model.

RESULTS

The median age of the patients was 52 yr. Ninety patients (63.6%) were female. The rate of patients older than 65 years was 19.7% (n: 28). The rate of open and laparoscopic cholecystectomy was 53.5% and 33.1%, respectively. Conversion to open cholecystectomy was performed in 19 patients (13.4%). The total rate of local and systemic complications was 7 % (n: 10). The median length of hospital stay was 7 days. Demographic data and clinical characteristics of the patients are shown in Table 1.

Eighty-four patients (59.2%) met the criteria for a definite diagnosis of AC according to Tokyo guideline 2013. All patients with a suspected diagnosis had grade 1 disease. Distribution of the patients with definite diagnosis according to disease severity was as follows; 57.1% grade 1, 36.9% grade 2, and 6% grade 3. Distribution and characteristics of the patients according to suspected and definite acute cholecystitis diagnosis are shown in Table 2.

Based on clinical severity; 74.6% of the patients had mild, 21.8% moderate, and 3.5% had severe disease. The rate of male patients within moderate and severe disease group was significantly higher. All patients with a suspected diagnosis had grade 1 disease. The rate of patients with a definite diagnosis in grade 2 and grade 3 groups were 37% and 6%, respectively. Patient characteristics and distribution according to Tokyo severity grading are demonstrated in Table 3 in details.

Table 1. Demographic data and clinical characteristics of the patients

	n	Percentage %	Mean±sd	Median	Min-max
Age	142		51±15	52	22-78
Age group					
≤65 yrs.	114	80.3			
>65 yrs.	28	19.7			
Gender					
Female	90	63.4			
Male	52	36.6			
ASA					
1	32	22.5			
2	103	72.5			
3	3	4.9			
Comorbidities					
Chronic Obstructive lung disease	3	2.1			
Congestive heart failure	3	2.1			
Diabetes mellitus	6	4.2			
Hypertension	4	2.8			
End stage renal Failure	1	0.7			
None	125	88			
Pre-op hospital stay	142		4.7±1.4	4.0	2-7
Post-op hospital stay	142		3.3±1.8	3.0	1-12
Total hospital stay	142		7.9±2.6	7.0	4-17
Time of operation	142		4.6±1.4	2.0	7.0
Diagnosis					
Suspected	58	40.8			
Definite	84	59.2			
Grade (according to TG 13)					
Grade 1	106	74.6			
Grade 2	31	21.8			
Grade 3	5	3.5			
Operation					
Laparoscopic	47	33.1			
Open	76	53.5			
Conversion	19	13.4			
Pathologic diagnosis					
Acute cholecystitis	42	29.6			
Phlegmonous Cholecystitis	6	4.2			
Gangrenous Cholecystitis	10	7			
Chronic Cholecystitis	84	59.2			
Antibiotherapy					
Cephazoline	59	41.5			
Cephazoline+ metronidazole	74	52.1			
Other (tigecycline, etc)	9	6.3			
Complications	10	7.0			
Surgical site infections	5	3.5			
Pulmonary infection	3	2.1			
Evisceration	1	0.7			
Biliary leakage	1	0.7			

Table 2. Distribution of patients according to definite and suspected diagnosis

	Suspected diagnosis (n: 58)	Definite diagnosis (n: 84)	p
Age	51.7±13.1	51.3±15.5	0.672
Age group			
≤65 yrs.	49	65	
>65 yrs.	9	19	0.204
Gender			
Female	47	43	
Male	11	41	0.001
ASA			
1	15	17	
2	42	61	0.283
3	1	6	
Comorbidities			
None	51	74	
COPD	1	2	
CHF	1	2	0.593
DM	2	4	
ESRD	1	0	
Hypertension	2	2	
Operation procedure			
Open	30	64	
Laparoscopic	24	16	0.075
Conversion	4	4	
Operation group			
In 3-5 days	45	54	
In 5-7 days	13	30	0.090
Time of operation	4.4±1.2	6.8±1.4	0.356
Complications			
Surgical site infection	0	5	
Pulmonary infection	2	1	0.120
Incisional hernia	0	1	
Biliary leakage	0	1	
Grade (according to TG 13)			
Grade 1	58	48	
Grade 2	0	31	
Grade 3	0	5	0.001
Pathology evaluation			
Acute cholecystitis	1	41	
Phlegmonous Ch	0	6	0.001
Gangrenous Ch	0	10	
Chronic Ch	57	27	
Antibiotherapy	28	31	
Cephazoline	25	49	0.183
Cephazoline+metronidazole others	5	9	
Post-op stay	2.9±1.3	3.6±2.1	0.047
Post-op hospital stay group			
1-4 days	48	64	
5-7 days	10	16	
More than 8 days	0	4	0.222
Total hospital stay	7.4±2.0	8.4±2.8	0.029

ASA Score: American Society of Anesthesiologiss score; TG 13: Tokyo guideline 2013; Ch: cholecystitis; COPD: chronic obstructive pulmonary disease; CHF: chronic heart failure; DM: diabetes mellitus; ESRD: end stage renal disease

Table 3. Distribution of patients according to Tokyo guideline severity grade

	According to Tokyo 2103 Guideline			
	Grade 1 (n: 106)	Grade 2 (n: 31)	Grade 3 (n: 5)	p
Age (yrs.) % (n)	49±15	55±14	63±8	0.493
Age group % (n)				0.283
≤65 yrs.	62 (88)	16 (23)	2 (3)	
>65 yrs.	13 (18)	6 (8)	1 (2)	
Gender % (n)				0.024
Female	52 (74)	10 (14)	1 (2)	
Male	23 (32)	12 (17)	2 (3)	
ASA % (n)				0.042
1	18 (26)	4 (6)	0 (0)	
2	55 (78)	15 (21)	3 (4)	
3	1 (2)	3 (4)	1 (1)	
Comorbidities % (n)				0.208
None	68 (96)	18 (26)	2 (3)	
COPD	0.7 (1)	0.7 (1)	0.7 (1)	
CHF	1.4 (2)	0.7 (1)	0 (0)	
DM	2.8 (4)	0.7 (1)	0.7 (1)	
ESRD	0.7 (1)	0 (0)	0 (0)	
Diagnosis (According to TG 13) % (n)				0.001
Suspected	41 (58)	0 (0)	0 (0)	
Definite	34 (48)	22 (31)	3.5 (5)	
Time of Operation (days) % (n)	4.4±1.3	5.3±1.4	5.8±1.6	0.004
Surgical procedure % (n)				0.014
Open	37 (53)	14 (20)	2 (3)	
Laparoscopic	30 (42)	2 (3)	1.4 (2)	
Conversion	8 (11)	6 (8)	0 (0)	
Operation group % (n)				0.001
3-5 days	58 (83)	10 (14)	1.4 (2)	
5-7 days	16 (23)	12 (17)	2 (3)	
Antibiotherapy % (n)				0.191
Cephazoline	33 (47)	8 (12)	0 (0)	
Cephazoline+Metronidazole	36 (51)	13 (18)	3.5 (5)	
Others (Tigecycline, etc.)	6 (8)	0.7 (1)	0 (0)	
Complications % (n)				0.392
Surgical site infection	2 (3)	0.7 (1)	0.7 (1)	
Lung infection	2 (3)	0 (0)	0 (0)	
Incisional hernia	0 (0)	0.7 (1)	0 (0)	
Biliary leakage	0.7 (1)	0 (0)	0 (0)	
Postop stay (days) % (n)	3.0±1.7	4.0±1.7	5.2±3.3	0.014
Postop hospital stay group % (n)				0.007
1-4 days	63 (90)	13 (19)	2 (3)	
5-7 days	10 (14)	8 (11)	0.7 (1)	
Over 8 days	1.4 (2)	0.7 (1)	0.7 (1)	
Total hospital stay (days) % (n)	7.4±2.4	9.3±2.2	11.0±2.6	0.001
Pathology evaluation % (n)				0.001
Acute cholecystitis	20 (28)	10 (14)	0 (0)	
Phlegmonous cholecystitis	0 (0)	3.5 (5)	0.7 (1)	
Gangrenous cholecystitis	0 (0)	6 (9)	0.7 (1)	
Chronic cholecystitis	55 (78)	2 (3)	2 (3)	

ASA: American Society of Anesthesiologists; TG 13: Tokyo guideline 2013; COPD: chronic obstructive pulmonary disease; CHF: chronic heart failure; DM: diabetes mellitus; ESRD: end stage renal disease

Table 4. Patient length of hospital stay according to surgical procedures

	Open cholecystectomy	Conversion group	Laparoscopic cholecystectomy	p
Postoperative stay (days)	3.7±1.5	3.8±1.8	2.6±2.1	0.001
Discharge in 1-4 days (%)	71	79	91	0.020
Total hospital stay (days)	8.6±2.3	8.5±2.1	6.8±2.7	0.001

In this study, no mortality was observed. There were no biliary complications in the open cholecystectomy group, while only one patient developed a biliary complication that was managed with medical treatment in the laparoscopic cholecystectomy group. The rate of postoperative local and general complications was 5% and 2%, respectively. Surgical operation was performed after a median of 4 days after hospital admission. There was no statistically significant correlation between time to operation and complications. Although length of hospital stay was higher in patients with complications, it was not statistically significant. Analysis of the factors associated with complications revealed histological diagnosis alone as a risk factor. Surgical site infection was more frequent in case of acute cholecystitis, while pulmonary complications were more frequent in patients with chronic cholecystitis. Conversion rate from laparoscopy to open surgery was determined as 13.4%. In multivariate analysis, only histological diagnosis (acute cholecystitis) was found as a risk factor to conversion (OR 0.19; 95% CI 0.07-0.41, p:0. 016).

Preoperative length of hospital stay was significantly higher in patients older than 65 years, those with high severity grades, and those who received combination antibiotherapy. ASA score, operation type, gender, diagnosis group, histologic diagnosis and presence of comorbidities or complications were not associated with preoperative length of hospital stay. On multivariate analysis, age older than 65 years (OR 4.21; 95% CI 3.53-4.90, p: 0.007), grade 3 disease (OR 5.20; 95%CI 1.04-9.36, p: 0.005), and combination antibiotherapy (OR 3.59; 95%CI 3.17-4.01, p:0.003) were identified as independent risk factors for preoperative length of hospital stay.

Postoperative length of hospital stay was longer in the open cholecystectomy group as compared to the laparoscopic group. The rate of patients discharged in 1-4 days were 71% in the open group,79% in the conversion group and 91% in the laparoscopic cholecystectomy group. Table 4 displays the differences between postoperative and total length of hospital stay according to surgical procedures.

Allocation of patients into groups according to preoperative duration of medical treatment (3-5days vs. 6-7 days) showed that while the conversion rate was higher in the 3-5 days group; patients older than 65 years, those with high grade disease (1.2±0.4, 1.5±0.6, p:0.001), those who have received combination antibiotherapy, and those with longer postoperative length of hospital stay (3±2, 3.8±1.5, p:0.045) were more frequent in the 6-7 days group. There was no statistically significant difference between the two groups with regard to age,

gender, ASA score, presence of comorbidities, complication rates, diagnosis according to TG 2013, and histologic diagnosis. On multivariate analysis, older age (OR 5.36; 95%CI 4.72-5.99, p:0.003), surgical procedure (conversion) (RO 4.68;95%CI 4.06-5.31, p:0.048), grade 3 disease (OR 5.80; 95%CI 3.76-9.84, p:0.001) and combination antibiotherapy (RO 5.11; 95%CI 4.76-5.45, p:0.002) were identified as factors related to duration on medical treatment in the preoperative period.

When the patients were further categorized according to preoperative time on medical treatment as those with 3 days or more than 3 days, no correlation was found with regard to age, gender, ASA score, surgical procedure, age group, antibiotherapy type, complication rate, diagnosis according to TG 2013, grade, histological diagnosis, postoperative and total length of hospital stay.

Higher ASA score, open cholecystectomy, patients with a definite diagnosis, high grade cholecystitis, patients older than 65 yr and acute, phlegmonous and gangrenous cholecystitis in histology evaluation were associated with longer postoperative hospital stay. On multivariate analysis, only old age (OR 4.21; 95%CI 3.53-4.90, p:0.001) and grade 3 disease (OR 5.20.95%CI 1.04-9.36, p:0.001) were identified as independent risk factors for longer postoperative hospital stay. (ASA score p:0.093, operation type p:0. 099, histologic diagnosis p:0.485, clinical diagnosis p:0.529). There was no correlation between postoperative hospital stay and gender, age, co-morbidities, complications and antibiotherapy.

Total length of hospital stay was longer in patients with older age, those older than 65 yr, those who received combined antibiotherapy, with histologic diagnosis of acute, gangrenous or phlegmonous cholecystitis, and who underwent open cholecystectomy. On multivariate analysis; age (OR 10; 95%CI 7.52-12.48, p:0.001), older age group (OR 9.64; 95%CI 8.77-10.51, p:0.001), combination antibiotherapy (OR 8.72; 95% CI 8.14-9.30, p:0.015) and grade 3 disease (OR 11.0; 95%CI 7.71-14.29, p:0.001) was related to longer total length of hospital stay. ASA score, gender, presence of co-morbidities or complications, and TG diagnosis (d no affect on total length of hospital stay.

DISCUSSION

In the 1990's, laparoscopic cholecystectomy was not indicated in patients with acute cholecystitis, open cholecystectomy was routinely performed in such circumstances (19). Interval cholecystectomy (performed 6-8 weeks after medical treatment) was suggested by some centers. Many multicenter randomized controlled trials demonstrated that early laparoscopic cholecystectomy yielded similar mortality, morbidity and conversion rates as compared to interval cholecystectomy (20-23). Recently, early laparoscopic cholecystectomy is suggested as the first line treatment in acute cholecystitis (11). Unfortunately, the rate of early cholecystectomy in patients with acute cholecystitis still remains low (15-40%) (14-16). In our hospital, the most preferred clinical application is interval cholecystectomy, except our group.

The mortality rate in early laparoscopic cholecystectomy was previously reported as 0.3-0.46% (24, 25). In the present study, no mortality or biliary tract injury was observed in the early open and laparoscopic cholecystectomy groups. The rate of conversion from laparoscopic to open cholecystectomy was reported as 9.9-31 % (24-29). The conversion rate in the present study was comparable with the literature (13.4%). The risk factors for conversion were previously defined as presence of symptoms longer than 72 hr and high C reactive protein levels (>11.5) (28). In contrast, it has also been reported that duration of symptoms did not influence the rate of conversion (30). Time to surgery was not identified as a risk factor for conversion in the present study. Only the histologic diagnosis of acute cholecystitis was found as a risk factor for conversion.

The studies evaluating complications of early laparoscopic cholecystectomy reported the rate of biliary tract injuries as 0.2-3.5% (10, 29). In the present study, intraoperative biliary tract injury was not observed. The rate of local complications (wound infection, hemorrhage, abscess etc.) and local-systemic complication rates are reported as 4.5% and 9-20.7% (10, 26, 28, 29). Comparable with the literature, the local and systemic complication rates in our study were determined as 5% and 2%, respectively. The only risk factor for developing local and systemic complications was histologic diagnosis of gangrenous cholecystitis. There was no correlation between the severity index according to Tokyo guideline and complications. Navez et al. (29) defined CBD migration and conversion as a risk factor for local complications, and ASA score and histological diagnosis of gangrenous cholecystitis was presented as a risk factor for systemic complications.

Not every patient with acute cholecystitis is suitable to undergo early laparoscopic cholecystectomy, severity assessment of acute cholecystitis should be taken into account while making this decision (11). Cehng et al. (31) reported that surgeons use the Tokyo severity index and Charlson comorbidity score when making the decision to perform early cholecystectomy. The rate of open and laparoscopic cholecystectomy in the early period varies among centers in the literature. In a multicenter study conducted in Belgium, the rate of open cholecystectomy was reported as 6.8% (29). Also, in a cohort study including 30.000 patients with acute cholecystitis aged older than 65 yr, the rate of open cholecystectomy was stated as 29% (32). In the present study, almost fifty percent of the patients underwent open cholecystectomy. Most of the open cholecystectomy operations were performed in the initial period of our routine early cholecystectomy experiences.

Tokyo guidelines for the management of acute cholecystitis and cholangitis were firstly described in 2007 (17). By the revision committee, these guidelines were improved by means of diagnosis and severity grading in 2013. Criteria for severity grading were adopted in clinical practice (11, 17). The diagnostic sensitivity rate was improved from 82.8% to 91.8%. The false positivity rate was reduced from 15.5% to 5.9% (17). In a study including 103 patients with acute cholecystitis who underwent early cholecystectomy, only 71.8% of the patients matched the diagnosis criteria (31). The sensitivity and validity of the Tokyo guidelines in the Turkish population has not been previously reported. In the present study, the rate of the patients matching the diagnosis criteria according to TG 13 was 59.2%. All patients with a definite diagnosis

were histologically reported as acute cholecystitis, while all patients with suspected diagnosis except one were (98%) in the chronic cholecystitis group. These data suggest that diagnostic criteria in TG 13 maybe applied in the Turkish population. Further multicenter studies are needed to validate these results.

Lee et al. (33) suggested that Tokyo guidelines are not useful in clinical practice for prediction of complications and mortality. In contrast, Cheng et al. (31) reported that length of hospital stay and complication rates correlated with Tokyo severity grading system. In addition to the Tokyo severity grading system, the Charlson's comorbidity score has an impact on clinical outcomes in patients with acute cholecystitis (31). In the present study, longer total hospital stay was observed in patients with high severity grade, but there was no correlation between morbidity and severity grade. These findings maybe attributed to the limited number of patients with grade 2 and 3 disease.

The length of hospital stay was previously reported to be longer in the open cholecystectomy group as compared to laparoscopic cholecystectomy, and in the conversion group as compared to the laparoscopy group (29). In a meta-analysis evaluating the clinical safety and results of early and late cholecystectomy, median length of hospital stay was reported as 5.4 days for early laparoscopic cholecystectomy (10). In the present study, median total hospital stay was 6.8 days. In another study comparing laparoscopic cholecystectomies in 72 hr and after 72 hr, postoperative hospital stay was found to be similar among the two groups (26). In this study, postoperative length of hospital stay in the group with laparoscopic cholecystectomy after 72 hrs. was determined as 2.4± 1.3 days. Comparable with the literature, this period was 2.6±2 days in the present study.

CONCLUSION

Increased severity index prolongs pre- and post-operative length of hospital stay. Early cholecystectomy in acute cholecystitis performed by experienced surgeons after 72 hours of admission and within 7 days maybe a feasible and safe procedure.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethic committee of Tepecik Training and Research Hospital.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.S.; Design - İ.S., Ö.Ç.; Supervision - İ.S., F.İ.; Data Collection and/or Processing - İ.S., M.K., Ö.E.; Analysis and/or Interpretation - İ.S., Ö.Ç.; Literature Search - İ.S., M.K., Ö.E.; Writing Manuscript - İ.S., Ö.Ç.; Critical Reviews - İ.S., F.İ.

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

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

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Turk J Surg 2017; 33: 87-90
DOI: 10.5152/turkjsurg.2017.3448

Publication rates of abstracts presented at the annual congress of the Turkish Society of Colorectal Surgery (years 2003-2011)

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ABSTRACT

Objective: The aim of our study is to examine the Publication Rate of Congress of Turkish Society of Colorectal Surgery meeting abstracts and determine the factors affecting publication rate.

Material and Methods: All presentations at Congress of Turkish Society of Colorectal Surgery congresses held in 2003, 2007, 2009, 2011 were retrospectively assessed. Manuscripts indexed in Google-Scholar database were included. The meeting year, study type, presentation type, title and time to publication of studies were assessed. Actual impact factor values were assessed to introduce the scientific power of the journals.

Results: Among a total of 614 abstracts presented at these congresses, 139 (22.6%) presentations were published in various medical journals. The publication rate was higher in oral presentations as group compared to poster presentations (29.7% vs. 19.5%) ($p<0.001$). Mean time to publication period was 20.4 (±21.1) months. 78 (56.1%) of published articles were published in SCI-E journals while 61 (43.9%) were published in non-SCI-E journals. Experimental studies had a higher Publication Rate in analysis of publication rate according to study type ($p<0.001$). Prospective clinical studies had a higher publication rate than retrospective studies. The journals in which oral presentations had been published had greater impact factor than journals in which poster presentations had been published ($p=0.02$). If published; prospective clinical studies were published in journals with greater impact factor than retrospective studies ($p=0.04$).

Conclusion: The quality of a meeting is correlated with the publication of abstracts accepted as presentations. Congress of Turkish Society of Colorectal Surgery congress is an efficient meeting for researchers, and have a lower PR as compared to international congresses while having a similar publication rate to equivalent scientific meetings. Being more selective during abstract acceptance should increase the Publication Rate and quality of Congress of Turkish Society of Colorectal Surgery congresses.

Keywords: Abstract, annual congress, Turkish Society of Colorectal Surgery, publication rate

Cite this paper as:
Meral UM, Urkan M, Alakuş Ü, Lapsekili E, İflazoğlu N, Ünlü A, Özmen P, Demirbaş S. Publication rates of abstracts presented at the annual congress of the Turkish Society of Colorectal Surgery (years 2003-2011). Turk J Surg 2017; 33(2): 87-90

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

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Received: 07.11.2015
Accepted: 25.12.2015

Available online at
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INTRODUCTION

A scientific congress is an environment in which physicians with the same specialty and other health staff participate in, the results of which is shared as abstracts, and in which ideas are exchanged with one another. The abstracts presented in scientific congresses (oral/poster) are evaluated by the commissions that are assigned by the congress scientific committee during the preparation period of the congress and it is decided if the studies will be accepted in the congress or not.

The publication of abstracts in national/international peer-reviewed journals after the congress is one of the indicators of the scientific value of the congress. In a Cochrane meta-analysis published in 2007, it was stated that the publication rate of the abstracts presented in a congress was 44.5% (1). Articles evaluating the conversion rate of the abstracts presented in international congresses into publications are limited. Similarly, the number of studies that are conducted in order to reveal the scientific efficiency of national congresses held in our country is also low. In these studies, it is reported that the conversion rate of the abstracts presented in the congresses to publications is very limited (between 5.7% and 28.6%) (2-7).

Turkish Society of Colorectal Surgery (TSCRS) organizes periodic scientific activities in order to develop the professional, scientific and social relationships between its members in accordance with its aims. The congresses of TSCRS, which are organized once in two years, are one of the important scientific activities. In our study, we aimed to define the conversion rate of the abstracts presented in the congresses organized in 2003, 2007, 2009 and 2011 to articles in peer-reviewed journals, to determine the factors (presentation type, study type, congress year etc.) effecting publication rate.

MATERIAL AND METHODS

The abstracts of oral presentations (OP) and poster presentations (PP) presented at the TSCRS congresses in 2003, 2007, 2009 and 2011 were extracted from the congress database. Since the congress in 2005

was organized in association with the International Society of University Colon and Rectal Surgeons – ISUCRS congress in 2006, abstracts of that congress were not included in the study. A database including certain characteristics of the abstracts such as presentation type (oral/poster), title, study type (clinic study, experimental study, case presentation, review) (prospective/retrospective) was established, and all abstracts that were included in the study were entered into this database individually. Abstracts were classified under ten different categories according to their subjects, and they were analyzed. Abstracts were then searched in Google Scholar (http://scholar.google.com.tr) database. The last date of this search was July 15th 2015. The first author's name and a key word in the abstract's title were used for searching. If the article could not be found then all authors' names were searched individually. Since both English and Turkish articles were searched in the database concurrently, entire key words were used in both English and Turkish. Even if there was a change in the number and sequence of the authors of the article, it was considered as having been published provided that there was no change in the hypothesis and sample of the study. In addition, provided that there was no change in the method and results of the study, the increase in the sample size was also considered as being published since it is assumed that a preliminary presentation had been done in the congress. The articles, the journal on which it was published in, date of publication, quality of the journals (Science Citation Index-Expanded (SCI-E)/out of SCI-E) were noted. The examination of each journal about their SCI-E status and their current impact factor (IF) were realized via www.researchgate.com (8). The duration between the date of the congress and publication date of the article was noted in months. The abstracts which have been published prior to the congress were also included in the study.

In a study evaluating the interval between presentation of an abstract in a congress and its publication in a peer-reviewed journal as an article, it was reported that 90% of the abstracts that have been published as articles were published within four years (9). Therefore, since we conducted our study in 2015, the TSCRS congress in 2011 was selected as the most current meeting. Since our study is a retrospective archive work, the approval of the ethics committee did not required. Also we did not use patient data in our study. The study did not require informed consent.

Statistical Analysis

After the database was entered into a computer, Statistical Package for the Social Sciences version 20.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Numerical data were evaluated with independent sample T-test and One-Way ANOVA test, and categorical data were evaluated with Pearson chi-square test and Fishers-Exact test. Numeric variables were presented as average and standard deviation, and categorical variables were presented as percentages. The results were assessed in 95% confidence interval and the results with <0.05 p value were considered as significant.

RESULTS

Six hundred and fourteen abstracts were presented in 4 congresses that had been organized between 2003 and 2011. Two hundred and nine (34%) of these abstracts were OPs whereas 405 (66%) were PPs. In the examination of study characteristics; 419 (68.2%) abstracts were clinic studies, 33 (5.4%) were experimental studies, 159 (25.9%) were case presentations, and 3 (0.5%) were reviews (Table 1). Ninety-seven (23.2%) of the clinical studies were prospective studies whereas 322 (79.6%) were retrospective in nature.

Table 1. Classification of the abstracts presented at congresses according to study type

Type of study	Total	Publication (+)	%	p
Clinical study	419	91	21.7	<0.001
Experimental study	33	19	57.6	
Case presentation	159	29	18.2	
Review	3	0	0	
Total	614	139	22.6	

Table 2. Average time until publication of the abstracts according to years

Year of congress	n	Average time until publication (months)	SD	Minimum	Maximum	p
2003	13	40.6	26.04	2	92	
2007	23	20.7	23.13	2	80	0.003
2009	45	18.3	22.41	-25	71	
2011	58	17.3	15.20	-33	50	
Total	139	20.4	21.06	-33	92	

SD: standard deviation

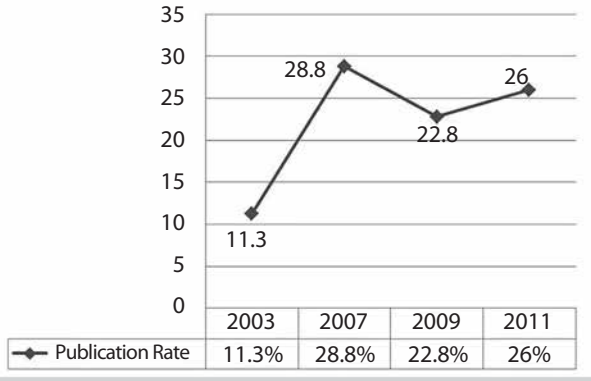

Figure 1. Publication rates of the abstracts according to years

One hundred and thirty-nine (22.6%) of 614 abstracts presented in the congresses were published as articles in 49 different journals that were listed by Google Scholar (http://scholar.google.com.tr) database. The distribution of publication rate according to years was found as: 13/115(11.3%) in 2003, 23/80(28.8%) in 2007, 45/197(22.8%) in 2009, and 58/223 (26%) in 2011 (Figure 1). While the publication rate of OPs was 28.7%, it was 19.5% for PPs (p=0.001).

The duration between the date of congress and the publication date of abstract as an article was compared according to years. While the publication duration of the abstracts was 20.4 month, this duration was 40.6, 20.7, 18.3 and 17.3 months for

Table 3. Classification of the published abstracts according to their subjects

Title	Publication (+)	Total	%	p
Appendix diseases	11	53	20.8	0.62
Hemorrhoidal disease	5	25	20	
Intraabdominal non-colorectal diseases	14	41	34.1	
Colonoscopy	3	17	17.6	
Colorectal tumors	35	160	21.9	
Laparoscopic colorectal surgery	7	24	29.2	
Perianal diseases	9	61	14.8	
Pilonidal disease	11	43	25.6	
Stomas	8	28	28.6	
Non-oncologic colorectal Diseases	36	162	22.2	
Total	139	614	22.6	

Table 4. The first 20 journals in which abstracts were published as articles (According to frequency)

	Name of Journal	Number of abstracts published	%	SCI/ SCI-E
1	Turkish Journal of Surgery	16	11.5	-
2	World Journal of Surgery	7	5	+
3	Diseases of Colon and Rectum	5	3.6	+
4	Journal of Diseases of the Colon and Rectum	5	3.6	-
5	Ulusal Travma ve Acil Cerrahi Dergisi	4	2.8	+
6	Gulhane Medical Journal	3	2.1	-
7	Indian Journal of Surgery	3	2.1	+
8	Int. Journal of Clinical and Experimental Medicine	3	2.1	+
9	Journal of Laparoendoscopic & Advanced Surgical Techniques	3	2.1	+
10	The American Journal of Surgery	3	2.1	+
11	The Turkish Journal of Gastroenterology	3	2.1	+
12	World Journal of Gastroenterology	3	2.1	+
13	Saudi Medical Journal	2	1.4	+
14	Asian Journal of Surgery	2	1.4	+
15	Journal of Gastrointestinal Surgery	2	1.4	+
16	Journal of Investigative Surgery	2	1.4	+
17	International Journal of Colorectal Disease	2	1.4	+
18	Hepatogastroenterology	2	1.4	+
19	The Medical Bulletin of Haseki	2	1.4	-
20	Clinics	2	1.4	+

SCI: Science Citation Index; SCI-E: Science Citation Index Expanded

the years of 2003, 2007, 2009 and 2011,respectively (Table 2). OP and PP abstracts were compared according to publication durations, but no significant difference was observed (p=0.17). When it was evaluated according to abstract subjects, "Non-Oncologic Colorectal Diseases" ranked first with 162 abstracts and "Colorectal Tumors" the second with 160 abstracts. When the publication rate was examined according to subjects, "Intraabdominal Non-Colorectal Diseases" had a PR of 34.1% whereas "Laparoscopic Colorectal Surgery" ranked second with a rate of 29.2%. Analysis of publication rate and publication duration according to subject revealed no significant difference (p=0.62, p:0.73 respectively) (Table 3). While 78 (56.1%) abstracts that have been published as an article were published in SCI/SCI-E journals, 61 (43.9%) were published in national/international journals that were not included within the SCI-E directory. It was determined that the journals in which the articles were mostly published are Turkish Journal of Surgery, World Journal of Surgery, and Diseases of Colon and Rectum along with Journal of Diseases of the Colon and Rectum (Table 4). When the publication rate was examined according to study type, it was seen that experimental studies had the highest rate of being published (p<0.001). When clinic studies were compared according to their prospective and retrospective nature, prospective clinic studies were converted to published articles more than retrospective studies. (38.1% and 16.8% respectively) (p<0,001). The abstracts which have been published in SCI/SCI-E listed journals were further examined for IF values of these journals. It was determined that the mean IF of the journals in which OPs have been published were higher than that of the journals in which PPs have been published (2.08 and 1.20, respectively) (p=0.02). It was determined that prospective clinic studies were published in the journals with higher IF values in comparison to retrospective studies (2.32 and 1.36, respectively) (p=0.04). Analysis of IF analysis according to study type (p=0.16) and congress year (p=0.78) revealed no significant difference.

DISCUSSION

The presentation of a study in national/international congresses enables transfer of newly discovered diagnosis/treatment methods to large scientific populations. On the other hand, the publication of studies in national/international peer-reviewed journals allows transfer of results to the whole scientific population without any limitations (10).

Six hundred and fourteen abstracts were presented in four TSCRS congresses that were included in this study, and 139 (22.6%) of these abstracts were published as articles in national/international peer-reviewed journals. In parallel with reports from meetings by similar societies, the quantity of OP abstracts are lower than PP abstracts' in TSCRS congresses. The reported overall publication rates vary from 5.7% to 58%. Kabay et al. (7) analyzed the publication rates of abstracts that were presented in National Surgery Congress between 1996 and 2004 as articles on peer-reviewed journals, and they stated that 5.7% of the abstracts have been published in international journals. This rate was determined as 22.6% in our study. The difference between the two studies was attributed to study methodology; the authors of the mentioned study have only used the PubMed search engine and thus have only included international journals that were indexed in that search engine into their study, while we used the Google Scholar (http://scholar.google.com.tr) database providing a larger search field. Therefore, the disparity does not indicate a quality difference between the two congresses. Yalçınkaya et al. (11) analyzed the abstracts that were presented at the 20th National

Turkish Orthopedics and Traumatology Congress in 2007, and although that was an international congress, they found the publication rate in international journals indexed in PubMed search engine as 29.5%. This high publication rate in that study was attributed to the fact that 52 of these abstracts were published on Acta Orthopaedica et Traumatologica Turcica, which is an SCI-E indexed Turkish journal. In our study, while 28.7% of the OP abstracts presented at TSCRS congress were published as articles, this rate was 19.5% for PP abstracts. Accordingly, the mean IF value of the journals in which OP abstracts have been published were significantly higher than that of the journals in which PP abstracts have been published. As pointed out by similar studies, this result which we have found about TSCRS congress abstracts suggests that; congress assessment commission has classified the abstracts as OP and PP, whereas the studies which are possible to be articles in higher quality journals were determined as OP and those with lower publication value were determined as PP. (4-7). In contrast, another study evaluating publication rate of the abstracts which have been presented at congresses organized by American Orthopedic Surgery Society reported that the publication possibility of the OP abstracts was similar to the publication possibility of the PP abstracts (52%-47%) (12).

Our publication analysis of abstracts were ended on August 2015, later analysis for relevant congresses of TSCRS abstracts may include additional data and change the present results. We considered this situation as a limitation against our study.

The publication rate of the abstracts that have been presented at the congresses and published as articles in SCI-E journals were analyzed along with their IF according to their prospective or retrospective study design. In parallel to literature, it was concluded that prospective studies are more important than retrospective studies due to their high publication rates and IF values. Publication of the congress abstracts in peer-reviewed journals is one of the pre-requisite conditions of certain scientific societies for "sending an abstract to a congress". However, such a pre-requisite does not exist for TSCRS congresses. In our study, we determined that 10 (7.2%) of the 139 abstracts were published as articles in /international peer-reviewed journals prior to the congress. It was determined that clinic studies constituted an important percentage of studies that were presented at the Turkish Society of Colorectal Surgery Congress, but that experimental studies have the highest publication rate as an article in peer-reviewed journals.

CONCLUSION

In conclusion, although the abstracts presented in Turkish Society of Colorectal Surgery Congresses yielded an equivalent publication rate with other similar organizations of similar scientific societies with its rate of 22.6%, this rate was lower in comparison with abstracts presented in international congresses. Being selective in the acceptance of abstracts to be presented at TSCRS congresses, and including the valuable studies into the congress may increase the publication rates of the abstracts.

Ethics Committee Approval: N/A.

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - U.M.M., A.A., M.U.; Design - N.I., A.U., U.M.M.; Supervision - P.O., U.M.M., S.D.; Resource - U.M.M., N.I.; Materials - E.L., U.M.M.; Data Collection and/or Processing - Ü.A., A.Ü.; Analysis and/or Interpretation - S.D., E.L., P.O.; Literature Search - Ü.A., M.U., A.Ü.; Writing Manuscript - E.L., N.I.; Critical Reviews - M.U., P.O., S.D.

Acknowledgements: The authors thank to Aylin Öztürk Meral M.D. for her support to our study.

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

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

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Turk J Surg 2017; 33: 91-95
DOI: 10.5152/turkjsurg.2017.3427

Xenotransplantation of human cryopreserved parathyroid tissue isolated from parathyroid adenomas to normocalcemic rabbits

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ABSTRACT

Objective: Parathyroid allotransplantation is a new method for the treatment of permanent hypoparathyrodism. Adenoma cells are not used for transplantation because of the potential for functional or histopathologic transformation. In this study, we transplanted human adenomatous parathyroid cells to rabbits.

Material and Methods: Parathyroid adenoma tissue taken from a male patient was cryopreserved and transplanted into seven New Zealand white rabbits (mean weight, 3700±220 g; mean age, 4.5 months) under immunosuppression. The levels of parathormone, calcium and phosphorus were measured before and after transplantation, and the parathyroid cells were observed histopathologically.

Results: Mean parathyroid hormone level was 0.5 pg/dL before transplantation and 6.6 pg/dL after transplantation ($p<0.05$). Preoperative mean calciumlevel was 14.1 mg/dL, and mean phosporus level was 3.5 mg/dL before transplantation while these values were 14.4 mg/dL and 3.3mg/dL, respectively, after transplantation ($p>0.05$). Morphologic transformation was not observed in parathyroid cells after transplantation.

Conclusion: In short-term observation, adenomatous parathyroid cells can function without malignant transformation. In the future, the preliminary methodology in this study may serve as a safe alternative for allotransplantation into patients with permanent hypoparathyroidism.

Keywords: Hypoparathyroidism, xenotransplantation, parathyroid adenoma

Cite this paper as:
Ayşan E, Düzköylü Y, Can İ, Büyükpınarbaşılı N. Xenotransplantation of human cryopreserved parathyroid tissue isolated from parathyroid adenomas to normocalcemic rabbits. Turk J Surg 2017; 33(2): 91-95

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Received: 19.10.2015
Accepted: 04.01.2016

Available online at
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INTRODUCTION

Hypoparathyroidism is a serious health problem that most commonly occurs as a complication of thyroid surgery. Postoperative hypoparathyroidism may be observed in three different variations such as transient (occurs within 3-6 months), protracted (occurs within 1 year) or permanent (occurs after the 1st year) (1). Because parathyroid hormone (PTH) has multiple metabolic functions, control of hypoparathyroidism symptoms with calcium (Ca) replacement therapy can be very difficult (2). Parathyroid allotransplantation for permanent hypoparathyroidism is a relatively new option for treatment (2-4). Upon extensive literature review, it is noted that donors are selected from cadavers or patients with secondary hyperparathyroidism. Primary parathyroid adenomas are the most common cases of surgical intervention indicated in the literature due to hyperparathyroidism, but these patients have not been used as donors thus far (5-7). Cells isolated from adenomatous parathyroid tissue are superior to healthy and secondary hyperplastic cells both in quantity and proliferation rate. However, because adenoma is a benign tumor, there are some concerns about its possible behavior in recipients (5, 6).The potential for functional or histopathologic transformation of adenoma cells is not yet known (5-7). In this study, we aimed to pre-evaluate the usability of this tissue with xenotransplantation from human to rabbit because it has potential to be quite valuable as a cell source.

MATERIAL AND METHODS

This research was performed in Bezmialem Vakif University, and the research protocol was approved by the same university's Local Animals Ethics Committee. All protocols were in accordance with the regulations governing the care and use of laboratory animals of the declaration of Helsinki.

Seven male New Zealand white rabbits (mean weight, 3700 220 g; 3700±220 g, mean age 4.5 months) without bred production were used. The rabbits were sheltered at one per cage in standard cages, with top and bottom parts made of stainless metal and sides made of woven wire. The floors of the cages were covered with wood shavings, which were changed daily. Rabbits were kept at room temperature and with adequate ventilation. Water and feeding containers were made of standard plastic, with sideways entrances. Animals were fed specially produced pellet feeds for small laboratory animals.

Procedure for Parathyroid Tissue Donor Patient: A 49-year-old male patient was admitted to the outpatient clinic with malignant hypercalcemia (blood calcium level >11 mg/dL). Ultrasound evaluation of the neck revealed a 3 cm diameter mass inferior to the left lobe of the thyroid tissue. Parathyroid scintigraphy (Tc 99m MIBI) indicated that the mass was a parathyroid adenoma. A small Kocher neck incision was performed, and the mass was excised and then divided into two parts. One part was used for histopathologic evaluation and the other part was cryopreserved according to thetechnique described below for xenotransplantation. The mass was reported as parathyroid adenoma inthe histopathologic evaluation.

Cryopreservation and Cell Preparation: Tissue was pooled and cryopreserved in three main steps: cell isolation, cell counting (total number of cells, rate of viability) and finally storing in a liquid nitrogen tank. Tissue samples were immediately placed in ice-chilled RPMI 1640 media after removal, and the cells were isolated. The entire protocol was carried out in sterile conditions in a sterile hood. All solutions and instruments were sterilized. The tissues were gently placed in a steel filter and rinsed with PBS+5% FCS (medium I). The tissues were then smashed with a syringe piston until the cells from whole tissues were split apart. The cells, floating in medium I, were filtered through a cell strainer. During these steps, some cells may lyse, releasing their DNA into the solution. This DNA can cause cell aggregation, which was prevented by the addition of DNase. Once whole tissue was disassociated and filtered through the cell strainer, Vi-Cell (Beckman Coulter) was used to determine viability with the trypan blue staining method. The cells were then prepared for cryopreservation with the following steps: a 500 µl FBS 20% DMSO (400 µl FBS+100 µl DMSO) solution was prepared and gently dropped into 500 µl FBS solution containing 0.25x106 cells on ice. The temperature of the solution was gradually decreased and the solution was then stored in a liquid nitrogen tank.

Transplantation: On the day of transplantation, 100 mg/kg prednisolon (Prednol-L 40 mg Ampul®; Mustafa Nevzat Co, İstanbul, Turkey) was used subcutaneously as an induction dose with a continued dose of 10 mg/kg/day for all rabbits. The cell solutions were thawed by submerging in a 37°C water bath. After shaving and antisepsis with povidone-iodine (Batticon 10g Pvp-iyot; Adekallaç, İstanbul, Turkey), 300,000 parathyroid cells were injected intramuscularly into the superior portion of the right back extremity of the rabbits, after the procedure injection area was signed with a marker pen. PTH, calcium (Ca) and phosphorus (P) levels were sampled on post-transplantation day 10. On day 10, rabbits were sacrificed and the signed injection fields were resected for histopathologic evaluation. Specimens were fixed in 70% alcohol, dehydrated, and embedded in paraffin wax. Sections were cut at a thickness of 5 mm, stained with hematoxylin, eosin and evaluated by a pathologist experienced in endocrinology.

Primary evaluation parameters of this research are histopathologic differentiation of transplanted cells and blood PTH, Ca, P levels. The occurrence of complications related to transplantation is the secondary evaluation parameter. We used human parathyroid hormone kit in our study, which shows results under 0.5 as 'zero' and results over 1900 as 'unidentified'.

Statistics Analysis: All statistics were performed using Statistical Package for the Social Sciences version 15.0 for Windows (SPSS Inc.; Chicago, IL, USA). Continuous variables are expressed as the means±standard deviation (SD). Significances of the measurements of serum calcium and phosphorus levels were evaluated by the Wilcoxon test. The differences were considered statistically significant if the p value was less than 0.05.

RESULTS

Levels of PTH, Ca and P in blood from the ear veins of the rabbits before and on the 10th day aftertransplantation before sacrificing are shown in Table 1. When the levels before and aftertransplantation were compared, the differences between the levels of PTH were statistically significant ($p<0.05$). While Ca levels had increased, P levels had decreased, but the differences for these twoparameters were not statistically significant. Mean PTH level was 0.5 pg/dL before transplantation and 6.6pg/dL after transplantation ($p<0.05$). Mean Ca level was 14.1 mg/dL, mean P level was 3.5 mg/dL before transplantation, and 14.4mg/dL and 3.3mg/dL, respectively, after transplantation ($p>0.05$). When parathyroid cells were observed histopathologically, there were no morphologic changesbefore and after transplantation (Figure 1, 2).

Table 1. Serum levels of PTH, Ca and P before and on the 10th day after xenotransplantation

Case	PTH (pg/dL) (before)	PTH (pg/dL) (after)	Ca (mg/dL) (before)	Ca (mg/dL) (after)	p (mg/dL) (before)	p (mg/dL) (after)
1	0.7	17.9	1 13.7	14	3.2	2.9
2	1.3	4.8	14.2	12.7	3	3.2
3	1.6	3.9	15	13.7	3.6	4.6
4	0	2	13.3	14	3.3	4
5	0	4.1	13.8	16.5	3.4	2.9
6	0	3.3	14.5	15.9	5	1.9
7	0	10.6	14.3	14.5	3.5	4
Mean	0.5	6.6	14.1	14.4	3.5	3.3

PTH: parathormone; Ca: calcium; P: phosphorus

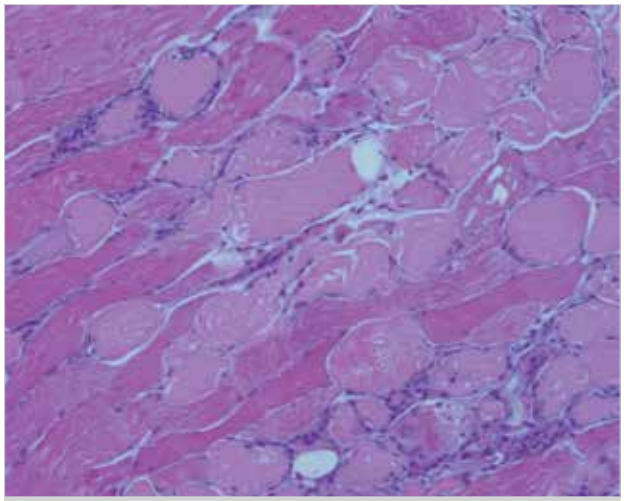

Figure 1. Parathyroid cells between the striated muscle fibers (Hematoxylin and Eosin, 40x magnification)

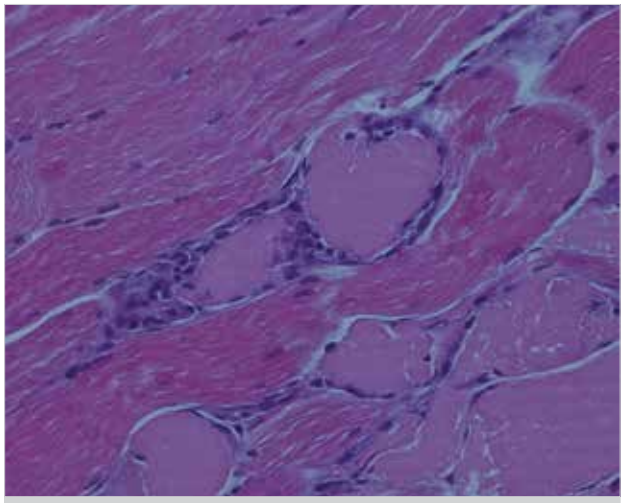

Figure 2. Parathyroid cells between the striated muscle fibers (Hematoxylin and Eosin, 200x magnification)

DISCUSSION

Because of the significant clinical symptoms of permanent hypoparathyroidism (PH), clinicians have studied various therapeutic solutions. In long-term medical treatment, oral calcium and vitamin D or its analogues can be administered. However, it is important to deliver them in appropriate doses with regards to pharmacodynamics, the potency at the tissue level, rapidity of action, and the ease of reversal of toxicity (8). Long-term treatment with calcium and vitamin D does not restore physiologic calcium homeostasis and often results in hypercalciuria, even in the face of normocalcemia, thereby increasing the risk of renal sequel (9). Additionally, the disadvantages of conventional therapy including a narrow therapeutic window, propensity for hypercalciuria and hypercalcemia, and the absence of negative feedback mechanisms have led to the investigation of new approaches, including parathyroid gland autotransplantation (8, 10, 11).

As has been shown in various studies, parathyroid gland autotransplantation is an effective approach for reducing the incidence of permanent and transient hypoparathyroidism and is best performed in the setting of total thyroidectomy (12-14). However, it is important to remember that this approach is only possible when the removal and/or devascularization of the glands is recognized by the surgeon peroperatively. Additionally, in patients who have been operated for secondary hyperparathyroidism, autograft hyperplasia may cause recurrences (15).

In recent years, surgeons have studied various therapeutic solutions for the treatment of PH based on other transplantation methods. In the literature, transplantation of parathyroid glands included in total laryngeal transplantation have been reported (16). Currently, studies involving iso-, allo-, and xenotransplantation of parathyroid tissue in human and animals indicate promising results that go far beyond the preoperative autotransplantation techniques (17, 18). The use of cultured human parathyroid cells is an essential technique for allo- and xeno- transplantation because it provides better engraftment of parathyroid cells by means of better revascularization and a decrease in the expression of the major histocompatibility complex on parathyroid cells (2, 19, 20). To overcome organ rejection in parathyroid allotransplantation, a number of methods have been proposed, such as short-term immunosuppression and immune-alteration by depletion of passenger leukocytes or preoperative organ culture but unfortunately, those approaches resulted in prolonged but insufficient graft function (21-23).

At present, tissues derived from patients with hyperplastic parathyroid glands are frequently used because of their numerous cells. Parathyroid hyperplasia is a clinical condition that is often coexistent with chronic renal failure (24-26). However, because the incidences of Hepatitis C and Hepatitis B viral infections in this patient population are high which prevent researchers from performing transplantations, even this limited number of patients cannot be used effectively as donors (27-30).

In the literature, it is shown that the average lifetime of these tissues derived from this donor population is no longer than 6 months, and this interval may be further prolonged in tissues derived from parathyroid adenoma (29). In this study, we transplanted adenomatous parathyroid cells from one human patient into rabbits and evaluated functional and histopathologic features. In each rabbit, increases in PTH levels were found to be statistically significant. Ca levels were also found to be increased and P were decreased, but the increase was not found to be statistically significant. These promising results show that, similar to theresults of studies with hyperplastic tissues, adenomatous transplants do not result in an uncontrolledincrease in either PTH or Ca levels. In addition, morphologic differences were not detected at theend of the study.

Although there are well-known published studies concerning transplantation of healthy parathyroid tissue to humans, there has not yet been a study about transplantation of adenomatous cells because of the malignant potential of parathyroid adenomas. In our experimental study, we evaluated the development and potential malignant transformation of adenomatous human parathyroid tissue transplanted into rabbits, with a successful combination of tissue culture passage and cryopreservation with immunosuppression.

Limitations of the study

Although our results were favorable, the effects were short-term. There are two reasons for this limitation. First, long-term immunosuppression in rabbits can lead to rapid metabolic disorders, which results in early deaths. Second, the cells that were transplanted in the muscle tissue could migrate from their initial localization, which may make histopathologic assessment impossible for us.

CONCLUSION

Our results show that adenomatous parathyroid cells function in the short-term without any morphologic transformation, which can support the consideration of a safe and alternative allotransplantation method of human adenomatous parathyroid tissue and may function as a preliminary work in this field of study.

Ethics Committee Approval: Ethics committee approval was received for this study from Bezmialem Vakıf University Animal Experiments Local Ethics Committee (Number 2013/99).

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

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

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

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

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Turk J Surg 2017; 33: 96-99
DOI: 10.5152/UCD.2016.3515

The outcomes of intestinal resection during debulking surgery for ovarian cancer

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ABSTRACT

Objective: To evaluate the clinical and surgical outcomes of intestinal resection during primary debulking surgery for ovarian cancer.

Material and Methods: This retrospective study was conducted at Zekai Tahir Burak Women's Health Training and Research Hospital between 2009 and 2013. The patients who underwent intestinal resection during debulking surgery for stage 3 ovarian cancer were included in the analysis. Data regarding patient age, body mass index, tumor histology, disease stage, the site of intestinal resection, all postoperative complications, duration of intensive care unit admission and hospital stay were collected and analyzed.

Results: A total of 22 patients with a mean age of 53.4 years were included in the study. Optimal cytoreduction was achieved in 14 (63%) patients. Transverse colectomy was the most common type of intestinal resection (63%). The most common postoperative complication was transfusion of blood products (63%). No postoperative mortality was observed.

Conclusion: Intestinal resection is a crucial part of debulking surgery for advanced ovarian cancer, with acceptable complication rates. Despite the limited number of patients, the results obtained from the present study are comparable with previous reports.

Keywords: Cytoreductive surgery, debulking surgery, intestinal resection, morbidity, ovarian cancer

INTRODUCTION

Ovarian cancer is the most lethal and the second most frequently diagnosed cancer among all gynecologic malignancies (1). Most ovarian cancers are epithelial neoplasms and tend to spread along peritoneal surfaces. Therefore, patients with ovarian cancer are often diagnosed at advanced disease stages with an average 5-year survival rate of approximately 30% (2, 3). Cytoreductive surgery followed by chemotherapy is the mainstay therapeutic approach and is considered to be the largest contributor of survival in advanced ovarian cancer (4). However, cytoreductive or debulking surgery is associated with high postoperative morbidity rates. There are several factors affecting morbidity rates such as age, general status of the patient, the presence of comorbidities, patient volume of the medical center, subtype of the tumor, and the extent of surgery (5). Intestinal surgery is usually indicated as part of debulking surgery to provide optimal tumor reduction among these patients, and is also responsible for increased postoperative morbidity (6, 7). Besides being a part of debulking surgery, intestinal surgery may be also needed for iatrogenic bowel injury or intestinal obstruction. In addition, bowel resection is often required for abdominal and pelvic recurrences and in palliation of intestinal obstruction (8).

In this study, we aimed to evaluate therapeutic outcomes and morbidity of intestinal resection during debulking surgery for stage III ovarian cancer.

MATERIAL AND METHODS

Patients

A total of 22 patients who underwent intestinal resection during debulking surgery for stage 3 ovarian carcinoma between 2009 and 2013 were included in this retrospective study. The ethics committee of Zekai Tahir Burak Women's Health Training and Research Hospital approved the study protocol. Informed consent was not taken from the patients due to the retrospective nature of the study. The data including patient age and body mass index (BMI), histology and stage of the tumor, the type of intestinal surgery, all postoperative complications, duration of intensive care unit (ICU) admission and hospital stay were collected from medical charts of the patients. The patients who only underwent appendectomy or intestinal surgery without resection were excluded from the study.

Cite this paper as:
Terzioğlu SG, Kılıç MÖ, Çetinkaya N, Baser E, Güngör T, Adıgüzel C. The outcomes of intestinal resection during debulking surgery for ovarian cancer. Turk J Surg 2017; 33(2): 96-99

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Received: 15.01.2016
Accepted: 14.03.2016

Available online at
www.turkjsurg.com

Study Design

All operations were performed by a single gynecological oncologist and a single general surgery team. Mechanical bowel cleansing and antibiotic prophylaxis were routinely administered to all patients on the day before surgery. All operations were performed via a standard midline abdominal incision. Gastrointestinal stapling devices were usually used for intestinal anastomosis. Rectosigmoid resection was performed in en bloc retroperitoneal approach method. In this technique as described earlier, the rectosigmoid colon was separated from the peritoneum and left pelvic wall by routine steps, and was divided using gastrointestinal stapling device (9). Optimal debulking was considered as the largest diameter of residual tumor equal to or less than 1 cm at the end of the surgery.

The Statistical Package for the Social Sciences (IBM Corp.; Armonk, NY, USA) version 21 was used for statistical analysis. Descriptive analysis was presented as mean±SD/percentage for continuous variables and number/percentage for categorical variables. $P<0.05$ was considered to be statistically significant.

RESULTS

The data of 22 consequent patients (mean age 53.4 years) who underwent debulking surgery with intestinal resection for stage III ovarian cancer were analyzed. Primary debulking was the unique indication for surgery. Optimal debulking surgery was achieved in 14 (63.7%) patients. Intestinal resection was performed to all patients because of tumoral spread to intestines. The most common type of intestinal resection was transverse colectomy (14, 63.7%). Anastomosis with an end-to-end technique was performed in the majority of patients (20, 90.9%). Colostomy was preferred in two patients (9.1%) who underwent low anterior resection for rectal involvement. As an indicator for blood loss, hemoglobin (Hb) change was calculated by subtracting postoperative Hb from preoperative Hb levels. The mean Hb change was 3.1 gr/dL. The demographic and clinical characteristics of the patients, surgical data, and pathological findings are presented in Table 1.

At least one postoperative complication was observed in 19 (86.4%) patients. The most common postoperative complication was transfusion of blood products, with an incidence of 63.6%. Two patients developed postoperative ileus; however, both had ability to pass flatus on the fifth day of the operation. Re-operation within the postoperative period was required in two patients. One of those patients underwent re-laparatomy for anastomotic leak on the 6th day of the operation, and colostomy was performed. The second patient had uncontrolled intestinal fistula, and thus the fistula tract was surgically removed on the 14th day of the surgery. All postoperative complications are presented in Table 2.

Pelvic abscess developed in one patient, and was successfully treated with antibiotherapy. The patient with pulmonary embolism was also treated medically with intravenous heparin. No mortality was observed postoperatively.

Table 1. Clinical characteristics of the patients who underwent intestinal resection during primary debulking surgery

Characteristics	n (%)
Age (y)	53.4±9.3
BMI	30.5±3.7
Albumin (gr/dL)	3.2±0.6
Preoperative Hb (gr/dL)	11.6±1.0
Postoperative Hb (gr/dL)	8.4±0.9
Hb change	3.1±0.9
Histological variant	
Serous	9 (40.9%)
Kruckenberg	5 (22.7%)
Endometriod	3 (13.6%)
Mucinous	3 (13.6%)
NET	2 (9%)
Type of intestinal resection	
Transverse colon resection	14 (63.7%)
Sigmoid colon resection	5 (22.7%)
Ileum resection	4 (18.1%)
Low anterior resection	2 (9%)
Operating time (min)	228.4±30.6
Oral intake (h)	6.0±2.4
ICU admission (d)	4.8±2.5
Hospital stay (d)	12.3±2.6

Histological variant, type of intestinal resection, optimal debulking, and hemorrhage were presented as n (%); the other variables were presented as mean±SD.
y: year; h: hour; min: minute; d: day; BMI: Body Mass Index; Hb: hemoglobin; NET: neuroendocrine tumor; ICU: intensive care unit

Table 2. Postoperative short- and long-term complications

Complications	n (%)
Transfusion of blood products	14 (63.6)
Surgical site infection	6 (27.3)
Atelectasis	4 (18.2)
Wound dehiscence	3 (13.6)
Ileus	2 (9.1)
Pulmonary embolism	1 (4.5)
Gastrointestinal fistula	1 (4.5)
Pelvic abscess	1 (4.5)

DISCUSSION

Primary optimal debulking surgery for ovarian cancer is traditionally defined as residual tumor less than one centimeter (10). However, debulking surgery has been recently classified as complete (without residual disease) and incomplete (with a residual disease at the end of the surgery) at the Gynecological Cancer Inter Group consensus conference in 2010 (11). Com-

plete resection of all macroscopic disease has been shown to be highly correlated with prolongation of the survival (12-15). Although the completeness of debulking surgery is the single indicator of survival of the patients with ovarian cancer, stage and histologic subtype of the tumor also have significant prognostic effects (5). Unfortunately, only one third of ovarian cancers can be detected at early stages and most patients have stage 3 or 4 disease at the time of diagnosis (16-18).

An extensive resection containing pelvic surgery, pelvic and abdominal lymphadenectomy, and abdominal surgery is usually performed during debulking surgery. Intestinal surgery is usually indicated for optimal debulking in the treatment of ovarian cancer in 20 to 100% of the patients (19). The potential role of intestinal resection on morbidity and oncological outcomes have been studied in many studies (20, 21). There is a consensus on the positive prognostic impact of intestinal surgery in the surgical treatment of advanced ovarian cancer. Also, optimal debulking surgery was shown to reduce postoperative ileus and ascites (22). Despite these advantages, surgery-related morbidity remains a major concern of debulking surgery for most surgeons. In debulking surgery, morbidity associated with intestinal surgery has been reported with an incidence rate of up to 20% (21). In our department, maximal debulking surgery including bowel resection is the standard surgical approach because of its promoting impacts on the survival.

In the literature, bowel resection during debulking surgery was reported up to 23% (23, 24). Tamussino et al. (23) reported that rectosigmoid resection was the most common intestinal resection during primary surgical treatment of ovarian cancer while colostomy was performed in only 2% of the patients. In contrast, the most common type of intestinal resection was transverse colectomy, and colostomy was only needed in 9% of the patients in the present study.

Clark et al. (25) reported that at least one or more perioperative complications occurred in approximately one third of the patients who underwent cytoreductive surgery with intestinal resection in their patient group. They also reported that the most common perioperative complications were cardiopulmonary events and small bowel obstruction. Fauci et al. (26) found that comorbidity was highly associated with readmission within 30 days of discharge, and small bowel obstruction/ileus was the most common reason for this entity. Cai et al. (27) also reported the major complication rate as 22% in their debulking surgery series. In that study, the patients who underwent bowel resection had a significantly higher median survival as compared with the patients with suboptimal debulking. In addition, the major complications such as ileus, intestinal fistula, and urinary tract fistula were found to be similar between those groups, indicating that morbidity following debulking surgery with intestinal resection seemed acceptable. In the present study, at least one or more complications occurred in 19 out of 22 patients. This rate may be considered as higher in comparison to previous studies. However, it should be noted that there is not a standard classification of morbidities in those studies, in which either minor or major complications were reported. On the other hand, all complications from mild to severe were reported in our study. In addition, colonic resections which are most frequently related to postoperative morbidity were more common in our case series, in comparison to small bowel resections. The leading morbidity was related to transfusion of blood products, with an incidence of 63%. However, complications related to intestinal resection, such as intestinal fistula, pelvic abscess, and ileus developed in the minority of patients. Similarly, Morice et al. (28) found transfusion rate to be 39% in patients with debulking surgery.

Type of intestinal resection may be considered to be associated with the development of postoperative complications. Colonic resections are generally believed to be related to higher morbidity rates more than small bowel resections. Bristow et al. (24) reported that transverse colectomy contributed to optimal cytoreductive surgery with an acceptable morbidity rate. In that study, gastrointestinal fistula was reported in 5.3% of the patients. In our study, two major complications directly related to intestinal resection (one postoperative acute complete bowel obstruction and one intestinal fistula) were observed during the follow-up period, consistent with the literature (20, 21).

It is well known that patients with advanced ovarian cancer are usually in the old or mid-old age population and have accompanying systemic diseases that result in increased postoperative complication rates. Additionally, aggressive debulking surgery in old patients were reported to be associated with increase in postoperative mortality (29). In our study, the mean age was 53 years, and approximately 30% of the patients had at least one accompanying systemic disease. However, no mortality was observed within the postoperative period.

Mean intensive care unit admission was 4.8 days in our study. Bristow et al. (24) reported that the mean duration of intensive care unit admission was 2.5 days. This may be explained with the high comorbidity rate in our study population.

CONCLUSION

Optimal debulking surgery is the mainstay treatment of advanced ovarian cancer, and is highly correlated with patient survival. Intestinal resection is one of the main components of this radical procedure, with acceptable complication rates. Despite the limited number of patients, the results obtained from the present study are comparable with previous reports.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Zekai Tahir Burak Women's Health Training and Research Hospital.

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

Peer-review: Externally peer-reviewed.

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

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

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

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Turk J Surg 2017; 33: 100-103
DOI: 10.5152/turkjsurg.2017.3439

Idiopathic granulomatous mastitis: an institutional experience

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ABSTRACT

Objective: To study idiopathic granulomatous mastitis with respect to its various clinical features, etiologic factors, treatment modalities and complications.

Material and methods: Retrospective study of all patients who were diagnosed with idiopathic granulomatous mastitis from 1st January 2006 to 31st December 2014 at Kasturba Hospital, Manipal, India (a tertiary care referral centre). The research was performed according to the World Medical Association Declaration of Helsinki. Informed consent was taken from the patient before invasive procedures including surgery. Data was analysed using the Statistical Package for Social Sciences version 16.0 wherever appropriate.

Results: 73 patients diagnosed with idiopathic granulomatous mastitis during the time period were included. One patient was a male (1.37%), rest were all females (98.63%). The mean age of presentation was 32.67 years (range 23 to 66 years). 70 patients (95.89%) were parous females. Average duration since last childbirth was 4.6 years (range: 3 months to 33 years). 8 patients (10.95%) were lactating. History of oral contraceptive pill use was present in 40 patients (54.79%). The right breast was affected in 44 patients (60.27%), and the left breast in 29 patients (39.73%). None of the patients had bilateral disease. The most common symptom was a painless lump (61.64%). Rest of the patients (38.36%) presented with features of a breast abscess. 19 out of 39 FNACs done (48.72%) were positive for granulomatous mastitis. 59 were primarily managed surgically (lumpectomy/ wide excision-33, incision & drainage-26). One patient was treated primarily with prednisolone. 13 patients did not receive specific treatment, and were only kept on regular follow-up. Patients managed with lumpectomy/ wide excision had the least rate of complications & recurrence (18.18%).

Conclusion: Patients with idiopathic granulomatous mastitis can present with a wide variety of symptoms which mimic other more common conditions. Surgical management in the form of wide excision appears to provide the best long term outcome in patients with idiopathic granulomatous mastitis.

Keywords: Idiopathic, granulomatous, mastitis

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic inflammatory condition of the breast. It was first described in 1972 by Kessler and Wolloch (1). Although it has been more than four decades since then the disease still remains an enigma. The etiology, natural course and treatment of choice of this condition are not yet well understood. Due to the rarity of the condition and the lack of sufficient studies, the prevalence of IGM is not known. Baslaim et al. (2) in their study reported that IGM represented 1.8% of 1106 cases of benign breast disorders which were subjected to a biopsy.

Idiopathic granulomatous mastitis typically presents as a lump in the breast with or without associated features of inflammation, in a parous woman of childbearing age. Clinically it may present with features similar to periductal mastitis (PDM). In fact, some authors consider IGM to be nothing but a variant of PDM (3, 4). The disease is usually unilateral, however, a few cases of IGM involving both breasts have been described (5). Diagnosis is further confounded by the fact that it often mimics carcinoma of breast, both clinically and radiologically (1, 6).

Histologically, a granulomatous inflammation is seen, which is closely related to the lobules. Granulomas composed of epithelioid histiocytes, Langhans giant cells accompanied by lymphocytes, plasma cells and occasional eosinophils are found within and around the lobules (7). The same cellular components are present in the FNA smears from these lesions (8). Histo-chemical stains for pathogens are usually negative. These findings have led to speculations of a cell mediated reaction to one or more substances in the mammary secretions of lobular cells, but no specific antigen has yet been identified (7).

Diagnosis of IGM is based on characteristic histological findings, after all possible infectious and non-infectious causes of granulomatous inflammation have been ruled out (1, 4, 9).

Cite this paper as:
Prasad S, Jaiprakash P, Dave A, Pai D. Idiopathic granulomatous mastitis: an institutional experience. Turk J Surg 2017; 33(2): 100-103

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Received: 02.11.2015
Accepted: 24.03.2016

Available online at
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There are no universally accepted guidelines available for management of IGM. Surgery (complete excision or incision and drainage), corticosteroids, immunosuppressant therapy and expectant management are some of the treatment strategies which have been described in literature. Several studies have shown varying degrees of success with all of these methods. Furthermore, management is complicated by a high rate of recurrence (16-50%) (9-11).

Herein, we describe our institutional experience with IGM over a period of 8 years.

MATERIAL AND METHODS

Medical records database of Kasturba Hospital, Manipal (a tertiary care centre) was searched retrospectively to identify all patients who were diagnosed with IGM between 1st January 2006 - 31st December 2014. The research was performed according to the World Medical Association Declaration of Helsinki. Informed consent was taken from the patient before invasive procedures including surgery. As it is a retrospective study, no separate consent was taken for inclusion in the study. For a patient to be included in the study, a histological diagnosis of granulomatous mastitis was required on core needle biopsy or open surgical biopsy. Furthermore, other causes of granulomatous mastitis had to be excluded. Finally, 73 such cases were identified and included in the study.

Patient characteristics, clinical features, etiologic factors, microbiologic studies, treatment modalities, complications and follow-up data for each patient were recorded and analysed. The variables were presented as mean, standard deviation, median, frequency and percent as appropriate. Data was analysed using the Statistical Package for Social Sciences version 16.0 (SPSS Inc.; Chicago, IL, USA).

RESULTS

During the study period, 73 patients were diagnosed with IGM in our hospital. Only one patient diagnosed with IGM was a male (1.37%), the rest were all females (98.63%). The mean age of presentation was 32.67 years, with a range of 23 to 66 years.

With the exception of three patients (including the one male patient), all the other patients (70; 95.89%) diagnosed to have IGM were parous females. Average duration since last childbirth in those 70 patients was 4.6 years (range: 3 months to 33 years). 8 patients were lactating at the time of presentation.

Two of the 73 patients were smokers (2.74%). History of oral contraceptive pill use at some point of time was present in 40 patients (54.79%). None of the patients had a history of tuberculosis, sarcoidosis, connective tissue disease or any other infectious disease which could cause granulomatous inflammation.

The right breast was affected by the disease in 44 patients (60.27%), and the left breast in 29 patients (39.73%). None of the patients had bilateral disease. The most common site affected was the upper outer quadrant of the breast (32.88%), followed by lower inner (21.92%), upper inner (19.18%), lower outer (13.69%) and central (12.33%) quadrants.

Table 1. Fine Needle Aspiration Cytology (FNAC) findings

Granulomatous mastitis	19
Acute inflammatory features	10
Suggestive of malignancy	1
Duct ectasia	1
Inconclusive	8

Table 2. Adjuvant treatment after surgical management

Surgery performed (total number)	ATT	Prednisolone
Lumpectomy/ wide excision (33)	9	2
I&D (26)	4	1

ATT: anti tubercular treatment; I&D: incision and drainage

The most common presenting feature of the disease was a painless lump (61.64%). Rest of the patients (38.36%) presented with features similar to a breast abscess. 26.03% patients had fever at the time of presentation.

Fine needle aspiration cytology (FNAC) was performed in 39 patients (53.42%), the findings are shown in Table 1.

Core needle biopsy and/or surgical excision specimens were sent for histopathologic examination in all cases, and were reported as granulomatous mastitis. Gram staining, bacterial culture and Ziehl-Neelsen staining were done for all patients to rule out infectious / tubercular mastitis.

All patients received antibiotics for variable time periods. The reason for antibiotic administration was either a suspected infectious pathology at the time of presentation or routine perioperative antibiotic coverage. The type, dosage and duration of antibiotic administration depended on the indication for antibiotic use and physician's personal preference.

59 patients underwent surgery as the primary treatment, 33 of them underwent lumpectomy/wide excision, and 26 underwent incision & drainage. One patient was treated primarily with steroids (prednisolone). 13 patients did not receive any specific treatment initially and were kept on regular follow-up. Some patients received adjuvant antitubercular therapy (ATT) or prednisolone after surgical management (Table 2).

The occurrence of complications after the primary treatment is shown in table 3. The patient treated primarily with prednisolone recovered completely, and had no complications at 6 month follow-up.

All 12 patients who developed recurrent/residual abscess were managed by I&D. 6 of them recovered completely after I&D, while the other 6 developed a persistent discharging

Table 3. Complications associated with various treatment modalities

Primary treatment (number of patients)	Residual/ Recurrent abscess	Recurrent/ Residual lump	Sinus	Ulcer	Mastalgia	Total number of complications
Lumpectomy/ wide excision (33)	3	-	2	-	1	6 (18.18%)
I&D (26)	7	7	5	2	2	23 (88.46%)
Prednisolone (1)	-	-	-	-	-	0
Expectant (13)	2	2	4	1	-	9 (69.23%)
Total	12	9	11	3	3	38

I&D: incision and drainage

sinus and had to undergo excision of the sinus tracts. All of these patients eventually recovered.

Out of the 9 patients who had a residual lump at 6 months after primary treatment, 4 underwent lumpectomy and 5 were kept on regular follow-up. All 4 patients who underwent lumpectomy for residual lump recovered completely. 4 out of 5 patients who did not receive any treatment for the residual lump continued to have the same lump at 1 year follow-up, while one patient's residual lump regressed without any treatment.

11 patients developed a persistent discharging sinus during 6 months of follow-up. 8 of them underwent excision of the sinus tracts and the adjoining diseased breast tissues. All 8 of them recovered completely and were asymptomatic at 10 month follow-up. 3 of the patients were managed conservatively with a course of antibiotics as per the culture/sensitivity report and then kept on regular follow-up. In these 3 patients, the disease had a longer, protracted course, but eventually they all recovered (mean: 15.66 months, range: 13-18 months).

3 patients who had an ulcer at the operated site on the 6 month follow-up were all managed with local debridement and subsequent wound closure with secondary suturing. None of them had any further complications. Mastalgia in 3 patients was managed symptomatically with analgesics.

DISCUSSION

Idiopathic granulomatous mastitis is an enigmatic condition. Even though it was described more than 40 years ago, due to the rarity of this disease; its etiology, natural history and optimal treatment remain poorly understood. The disease is particularly troublesome for the patient because of its stubborn tendency to recur. Autoimmunity, pregnancy, lactation, hyperprolactinemia, oral contraceptive use, local trauma to the breast, alpha-1 antitrypsin deficiency and smoking have all been described as risk factors for the occurrence of the disease (12-16).

A favourable response of the disease to steroids and immunosuppressant drugs has pushed forward the hypothesis of autoimmune nature of the disease. The etio-pathogenesis of the disease is thought to involve the following sequence of events: ductal epithelial damage, transition of luminal secretions to the lobular connective tissue, local inflammation in connective tissue, macrophage and lymphocyte migration to the region, and local granulomatous inflammatory response (14). However, the cause of ductal epithelial damage has not been recognized.

According to literature, IGM typically affects parous females in the reproductive age group (1, 12, 13, 17-19). These findings were confirmed in our study, although there were exceptions. 2 patients diagnosed with IGM were young nulliparous females, whereas there was also a post-menopausal lady suffering from the same disease. But the biggest exception, perhaps, was the diagnosis of IGM in a male patient. Previously, only one case of IGM in a male patient has been reported in the literature (20). 54.79% patients had a history of use of OCPs, which is much higher than that reported in other studies.

The most common presenting symptom of patients with IGM was found to be a painless lump in the breast. FNAC as a tool for diagnosing IGM was not very efficient, as it had a high false-negative rate (51.28%).

Most of the patients in the current study were managed primarily surgically. Wide excision/ lumpectomy was found to be the most effective treatment option, having the lowest rate of recurrence and complications. Surgical management with I&D and expectant management were found to have an unacceptable high rate of complications and recurrence. Only one patient was managed primarily with steroids, and she recovered completely, with no recurrence or complications.

Expectant line of management with close follow-up was not found to be a satisfactory treatment option for IGM in the current study.

Study limitation

Due to the lack of adequate number of cases treated primarily with steroids, a satisfactory conclusion could not be drawn from the present study.

CONCLUSION

With 73 cases, this is one of the largest case series of Idiopathic granulomatous mastitis. The study reaffirms that this is a condition which is not easily understood. The patients can present with a wide variety of symptoms which mimic other more common conditions. Surgical management in the form of wide excision appears to provide the best long term outcome in patients with IGM. Although the use of corticosteroids has been advocated by some researchers, our experience with the same was limited to just one patient, hence we could not give a definite opinion on the same.

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

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

Peer-review: Externally peer-reviewed.

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

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

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

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Turk J Surg 2017; 33: 104-109
DOI: 10.5152/UCD.2016.3534

Prognostic factors in patients with acute mesenteric ischemia

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ABSTRACT

Objective: Acute mesenteric ischemia, one of the causes of acute abdominal pain due to occlusion of the superior mesenteric artery, has a fatal course as a result of intestinal necrosis. There is no specific laboratory test to diagnose acute mesenteric ischemia. The basis of treatment in cases of acute mesenteric ischemia is composed of early diagnosis, resection of intestinal sections with infarction, regulation of intestinal blood flow, second look laparotomy when required, and intensive care support. The aim of this study is to investigate the factors affecting mortality in patients treated and followed-up with a diagnosis of acute mesenteric ischemia.

Material and Methods: Forty-six patients treated and followed-up with a diagnosis of acute mesenteric ischemia between January 1st, 2008 and December 31st, 2014 at the General Surgery Clinic of our hospitalwere retrospectively evaluated. The patients were grouped as survivor (Group 1) and dead (Group 2). Age, gender, accompanying disorders, clinical, laboratory and radiologic findings, duration until laparotomy, evaluation according to the Mannheim Peritonitis Index postoperative complications, surgical treatment applied, and type of ischemia and outcome following surgery were recorded.

Results: A total of 46 patients composed of 22 males and 24 females with a mean age of 67.5±17.9 and with a diagnosis of mesenteric ischemia were included in the study. Twenty-seven patients died (58.7%) while 19 survived (41.3%). The mean MPI score was 16.8±4.7 and 25.0±6 in Group 1 and Group 2, respectively, and the difference between the two groups was statistically significant (p<0,001). Fourteen of the 16 (51.9%) patients who had a Mannheim Peritonitis Index score of 26 or higher died while two of them survived (10.5%). Thirteen out of the 30 (48.1%) patients with a Mannheim Peritonitis Index score of 25 or lower died while 17 (89.5%) patients survived. The increased MPI score was significantly correlated withmortality (p=0.004).

Conclusion: Suspicion of disease and early use of imaging in addition to clinical and laboratory evaluations are essential in order to decrease mortality rates in acute mesenteric ischemia. Prevention of complications with critical intensive care during the postoperative period aids in decreasingthe mortality rate. In addition, using the Mannheim Peritonitis Index can be helpful.

Keywords: Mannheim, mesenteric ischemia, prognostic factors

Cite this paper as:
Yıldırım D, Hut A, Tatar C, Dönmez T, Akıncı M, Toptaş M. Prognostic factors in patients with acute mesenteric ischemia. Turk J Surg 2017; 33(2): 104-109

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Received: 20.02.2016
Accepted: 26.04.2016

Available online at
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INTRODUCTION

Acute mesenteric ischemia (AMI), one of the causes of acute abdominal pain due to occlusion of the superior mesenteric artery, has a fatal course as a result of intestinal necrosis (1). AMI comprises 1% of all patients admitted to the hospital with acute abdominal pain, and is the etiology in 0.1% of patients who present to emergency departments (2, 3). The mortality rate in AMI remains high due to challenges in early diagnosis, the lack of specific markers, and irreversible intestinal ischemia secondary to delay in diagnosis. Although significant advances in its diagnosis and treatment have been madeover the last decade, mortality rates are still reported to be around 40-70% for acute mesenteric ischemia mainly due to a low index of suspicion. Early diagnosis and commencing appropriate treatment is essential in AMI. A delay of twenty-four hours can decrease survival by 20%. Therefore, the development of new diagnostic methods is extremely important (1-5).

The etiologic cause in 70-80% of cases with AMI is intestinal ischemia that occurs as a result of occlusion of the mesenteric artery due to an embolus or thrombus. Embolic occlusion results in earlier ischemia and transmural necrosis as compared with other causes, due to the absence of a well-developed collateral circulation (6). Strangulated hernia, venous thrombosis, and non-occlusive causes are rare reasons ofAMI. Individuals with a prior history of arterial embolus, vasculitis, deep venous thrombosis, and postprandial pain constitute thehigh-risk group (7).

Diagnosis of AMI is based on clinical suspicion and clinical findings. In AMI, severe abdominal pain is present disproportionate with the findings of a physical examination. Intestinal ischemia progresses transmurally, and in most cases peritonitis and sepsis has already ensued by the time of diagnosis, and

the role of imaging modalities is limited (8). Direct radiography and abdominal ultrasonography are non-diagnostic and abdominal computed tomography has a low sensitivity and specificity (9, 10). Although mesenteric vessels are visualized with an abdominal MRI, studieson the reliability of the results are limited. The American Society of Gastroenterology practice guidelines (2000) defined angiography as the gold standard for mesenteric ischemia (11). However, catheter angiography is invasive and time consuming. Furthermore, it is unavailable in many hospitals. Over the last decade, computed tomography-angiography (CTA) has replaced angiography as the gold standard in the diagnosis of mesenteric ischemia with a sensitivity and specificity of 0.86% and 0.94%, respectively, since it is less invasive and can be performed in a shorter time (12, 13). There is no specific laboratory test for acute mesenteric ischemia.

The basis of treatment in cases of acute mesenteric ischemia is composed of early diagnosis, resection of the intestinal sections with infarction, regulation of intestinal blood flow, second look laparotomy when required, and intensive care support (1).

The aim of this study is to investigate the factors affecting mortality in patients treated and followed-up with a diagnosis of AMI.

MATERIAL AND METHODS

Forty-six patients treated and followed-up with a diagnosis of AMI between January 1st, 2014 and December 31st, 2014 at the General Surgery Clinics of our hospital were retrospectively evaluated. The patients were grouped as survivors (Group 1) and dead (Group 2). Age, gender, accompanying disorders, clinical, laboratory and radiologic findings, duration until laparotomy, evaluation according to the Mannheim Peritonitis Index (MPI), postoperative complications, surgical treatment applied, type of ischemia, and outcome following surgery were recorded. In the patients who underwent operations, a second look laparotomy was performed within 12-48 hours. This decision was made by the surgeon who had performed the first operation and for the following reasons: in cases of suspicion of recurrent ischemia in the remaining intestinal segments after resection, if the line of demarcation was unclear or if ischemic changes were detected at the tip of the stoma created at the time of resection.

An ethics committee approval was obtained along with written informed consent from patients who participated in this study.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 17.0 (SPSS Inc.; Chicago, IL, USA). Descriptive statistics were expressed as number and percentage for categorical variables and mean and standard deviation for numerical variables. Comparisons of independent two groups were made by using the Student-t Test where numerical variables were normally distributed and using the Mann Whitney U test when they were not normally distributed. More than two-group comparisons of independent numerical variables were performed by using the One Way Anova test when variables were normally distributed and the Kruskal Wallis test when they were not normally distributed. Subgroup parametric analyses were made with the Tukey test and nonparametric tests were made with the Mann Whitney U test and interpreted with the Bonferroni correction. Categorical variables were tested using the Chi-Square test. The statistical alpha level of significance was accepted as $p<0.05$.

RESULTS

A total of 46 patients, composed of 22 males and 24 females with a mean age of 67.5±17.9, with a diagnosis of mesenteric ischemia were included in the study. Twenty-seven patients died (58.7%) while 19 survived (41.3%). The mean age ofthe patients who died and survived was 71.3±12.2 years and 61.7±23.2 years, respectively. There was no statistically significant difference in terms of gender between the groups (p=0.161 and p=0.329 respectively).

There was no statistically significant difference in the interval between the onset of complaints and presentation to the hospital between the two groups (30.9±23.8 hours in Group 1 and 27.7±20.7 hours in Group 2 (p=0.675).

D-dimer, WBC and pH values in Group 1 and Group 2 were 20220±9706 and 16002±6176, 4757±4603 and 5389±2246, and 7.4±0.0 and 7.3±0.2, respectively, and there was no statistically significant difference in laboratory parameters between the two groups (Table 1). Abdominal pain, nausea and vomiting, diarrhea, hematemesis and melena was found to be present in 44 (95.7%), 32(69.6%), four (8.7%), three (6.5%) and two (4.3%) patients, respectively. No statistically significant differences were present between the two groups in terms of symptoms, accompanying diseases, and CT findings (Table 2).

Arterial and venous occlusion was detected in 34 (73.9%) and eight (17.8%) patients, respectively, and four patients (8.9%) had non-occlusive disease. Thirty-eight patients (82.6%) underwent surgery. Thirty-two patients underwent resection, while six patients (13%) did not receive an intestinal resection. One patient underwent revascularization. No statistically significant difference was found in the type of ischemia between the groups (p=0.690).

Postoperative complications, in order of frequency, were ostomy creation in 23 patients (60.5%), short bowel syndrome in 16 patients (42.1%), wound site infection in ten patients (26.3%), sepsis in nine patients (23.7%), intra-abdominal abscess in six patients (15.8%), entero-cutaneous fistula in two patients (5.3%), and open abdomen in two patients (5.3%). Duration of intensive care stay was 5.9±9.8 days (median3 days).

The percentage of patients who underwent an operation was 77.8% (n=14) and 88.9% (n=24) in patients who survived and who died, respectively. There was no statistically significant difference in the rate of operation between the two groups (p=0.694). The type of operations in the two groups were similar (p=0.111). The rates of wound site infection and sepsis were statistically significantly higher in the patients who died as compared with the patients who survived (p=0.034 p=0.007) (Table 3).

Second look operations were performed on eight patients. Second look operations did not correlate with mortality

Table 1. Laboratory parameters of the two groups

	Survived	Died	p
Laboratory value			
AST	64.6±134.7	90.9±264.7	0.214
ALT	31.3±20.7	45.1±95.9	0.311
Total Bilirubin	1.3±1.2	1.5±0.8	0.097
Calcium	9.3±0.8	9.0±0.9	0.163
Sodium	137.9±5.4	137.5±4.9	0.795
Potassium	4.4±0.6	4.2±0.9	0.329
Amylase	85.9±60.2	141.5±140.5	0.511
Wbc	20220.0±9706.8	16002.3±6176.6	0.101
Neutrophil	82.3±10.6	77.3±14.7	0.398
Lymphocyte	10.5±9.2	12.2±10.5	0.823
Neutrophil/ Lymphocyte	18.1±27.7	14.4±14.7	0.709
Hg	13.5±2.4	13.3±2.5	0.822
Htc	41.6±6.2	40.4±7.1	0.582
Platelet	303647.1±184947.6	251276.9±105269.9	0.691
MPV	9.4±1.4	18.0±44.9	0.728
RDW	15.4±2.0	14.9±2.0	0.434
CK	649.9±1308.9	248.6±329.5	0.833
CKMB	79.5±217.1	9.6±13.0	0.973
Troponin	1.6±4.2	0.4±1.0	0.471
LDH	521.0±363.7	428.3±242.5	0.334
Lactate	5.6±4.8	7.6±3.7	0.430
D-dimer	4757.7±4603.7	5389.5±2246.7	0.817
HDL	34.9±19.2	30.6±16.9	0.531
LDL	92.9±56.7	83.5±47.8	0.636
Triglyceride	108.6±48.3	176.0±102.7	0.106
VLDL	20.7±9.6	33.4±19.7	0.108
Total cholesterol	150.0±74.2	149.2±57.9	0.975
pH	7.4±0.0	7.3±0.2	0.156

AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC: white blood cell; Hg: hemoglobine; Htc: hematocrit; MPV: mean platelet volume; RDW: red cell distribution width; CK: creatine kinase; CK-MB: creatine kinase-MB; LDH: low density lipoprotein; HDL: high density lipoprotein; VLDL: very low density lipoprotein

Table 2. Patient symptoms and CT findings

		Survived		Died		
		n	%	n	%	p
Symptoms	Tenderness	17	94.4	23	85.2	0.634
	Guarding	10	55.6	17	63.0	0.619
	Rebound tenderness	4	22.2	13	48.1	0.079
	Gastric pain	18	100.0	25	92.6	0.509
	Hypoactive bowel sounds	8	44.4	15	55.6	0.465
	Nausea	13	72.2	19	70.4	0.893
	Constipation	4	22.2	7	25.9	1.000
	Anorexia	13	72.2	22	81.5	0.489
	Diarrhea	1	5.6	3	11.1	0.640
	Hematochezia	2	11.1	1	3.7	0.555
	Melena	0	0.0	2	7.4	0.509
Accompanying diseases	Hypertension	11	61.1	20	74.1	0.357
	Diabetes	2	11.1	9	33.3	0.156
	COPD	6	33.3	11	40.7	0.616
	Cerebrovascular events	6	33.3	5	18.5	0.304
	Atrial fibrillation	8	44.4	15	55.6	0.465
	CAD	9	50.0	17	63.0	0.388
CT	Normal	3	27.3	3	20.0	1.000
	Free fluid	4	36.4	9	60.0	0.234
	Thickened bowel wall	7	63.6	10	66.7	1.000
	Thickened bowel wall+ Free fluid	3	27.3	7	46.7	0.428
	Free air	11	0.0	15	0.0	-
	Air fluid level	4	36.4	9	60.0	0.234

COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; CT: computed tomography

(p=0.141). Anastomosis following resection was performed in ten patients. Statistically, the mortality rate in patients who had undergone anastomosis was significantly lower (p<0.001).

Ischemia was detected in only the small intestine in 24 patients, while both the small intestine and colon were ischemic in 12 patients. The presence of colonic ischemia did not effect mortality (p=0.325).

The mean MPI score was 16.8±4.7 and 25.0±6 in Group 1 and Group 2, respectively, and the difference between the two groups was statistically significant (p<0.001). Fourteen of the 16 (51.9%) patients who had a MPI score of 26 or higher died while two of them survived (10.5%). Thirteen of 30 (48.1%) patients who had a MPI score of 25 or lower died while 17 (89.5%) patients survived. The increased MPI score significantly effected mortality (p=0.004).

DISCUSSION

Controlled randomized studies in the literature on acute mesenteric ischemia (AMI) are limited n number due to the low incidence and wide spectrum of the disease. A large majority of these studies, like ours, have a retrospective design (14,15). The absence of a specific method for the diagnosis of AMI generally results in delayed diagnosis. Mortality rates have been reported in different studies between 30% and 100%, and in this study the rate was found to be 60% (16-19).

An arterial embolus or thrombus in the superior mesenteric artery is the cause of intestinal ischemia in 70-80% of cases.

Table 3. Type of ischemia, operation and postoperative complications

		Survived		Died		
		n	%	n	%	p
Types of ischemia	Arterial occlusion	12	66.7	22	81.5	
	Venous occlusion	4	22.2	4	14.8	0.690
	Non-occlusive mesenteric ischemia	2	11.1	2	7.4	
Operation		14	77.8	24	88.9	0.694
	No resection	0	0.0	6	22.2	0.111
	Resection	14	77.8	17	63.0	
	Revascularization	0	0.0	1	3.7	1.000
Postoperative	Short bowel syndrome	6	33.3	10	37.0	0.799
	Wound site infection	1	5.6	9	33.3	0.034*
	Intra-abdominal abscess	0	0.0	6	22.2	0.067
	Ostomy	8	44.4	15	55.6	0.465
	Sepsis	0	0.0	9	33.3	0.007*
	Entero-cutaneous fistula	0	0.0	2	7.4	0,509
	Open abdomen	0	0.0	2	7.4	0,509

Less frequently, ischemia is due to a venous thrombus or non-thrombotic mechanical causes (5). In this present study, arterial occlusion was present in 73.3%, venous occlusion in17.8%, and non-occlusive mesenteric ischemia (NOMI) in 8.9% of cases. There was no statistically significant difference between the group of patients who died and who survived in terms of types of ischemia (p=0.690).

Although clinically not significant, the classical triad of abdominal pain, fever and blood in the stool is present in one third of cases (20). In this present series, abdominal pain, nausea and vomiting, diarrhea, hematemesis and melena were present in 44 (95.7%), 32 (69.6%), four (8.7%), three (6.5%) and two (4.3%) patients, respectively.

Peritonitis and septicemia, when developed, progresses transmurally. Various scoring systems have been used to evaluate the prognosis of peritonitis. In some studies, The Mannheim Peritonitis Index (table 4) has been reported as a reliable risk stratification system. The cut-off value for MPI was reported as 26, and mortality has been reported to significantly increase with higher scores (21-24). In this present study, we evaluated the predictive role of MPI scoring system. The mean MPI score was found to be significantly higher in Group 2 as compared to Group 1. In addition, an MPI score of 26 or higher significantly correlated with mortality.

In many studies, early diagnosis and treatment has been demonstrated to be the most effective criterion effecting mortality. Kassahun et al. (4) reported in their study that the survival rate was 30% lower in patients who were diagnosed 24 hours after the start of the symptoms. Among our patients, 24 were diagnosed during the 24 hour-period following the onset of symptoms, and treatment was started. Of these patients, 13 (54.2%) died and 11 survived (45.8%). Among the remaining 22 patients who were diagnosed and treated 24 hours later than the start of symptoms, 14 (63.6%) died and eight (36.4%) survived. Even though there are many studies reporting that early diagnosis and commencement of treatment in the first 24 hours decreases mortality, in this present study no statistical difference was detected (25-27).

Table 4. Mannheim Peritonitis Index

Risk Factor	Weighting if present
Age >50 years	5
Female sex	5
Organ failure	7
Malignancy	4
Preoperative duration of peritonitis>24 h	4
Origin of sepsis not colonic	4
Diffuse generalized peritonitis	6
Exudate	
Clear	0
Cloudy, Purulent	6
Fecal	12
Definitions of organ failure	
Kidney	Creatine level >177µmol/L Urea level>167 mmol/L Oliguria <20 ml/h
Lung	PO2<50 mmHg PCO2>50 mmHg
Shock	Hypodynamic or hyperdynamic
Intestinal obstruction	Paralysis >24 h or complete mechanical obstruction

PO2: partial pressure of oxygen; PCO2: partial pressure of carbon dioxide

Although AMI is generally seen in the elderly population, old age has been reported to be a negative prognostic criterion in some studies (28, 29). However, in this present study, no statistically significant difference was detected in the mean age between the two groups (p=0.161).

In some studies in the literature, it has been reported that accompanying disease is one of the risk factors for mortality (28, 30, 31). In a study by Alhan et al. (14), the accompanying disorders were reported to beatrial fibrillation in 78.5% of the patients, hypertension in 76.6%, congestive heart disease in 70%, and coronary artery disease in 40.2% of the cases, while in our study atrial fibrillation, hypertension, coronary artery disease and COPD was present in 23 (50%), 31 (67.4%), 26 (56.5%) and 17 (37%) patients, respectively. Presence of comorbidities did not significantly affect mortality in the present or the aforementioned study.

Laboratory values

Increases in the leukocyte count, urea, creatinine and amylase levels, and acidosis have been considered as predictors of mortality in different studies (19, 31-35). Although statistically not significant, in some studies mortality was found to increase in cases with leukopenia and this was explained as the result of a decreased or removed preventive effect of the immune system (36). D-dimer, a fibrin product occurring due to an enzymatic breakdown during intravascular coagulation and lactate levels, can also be increased in cases of AMI and in some other diseases (37). In this present study, levels of lactate and D-Dimer were found to have increased in patients with AMI, although their prognostic effect could not be demonstrated. Furthermore, in this present study, no significant differences were found in the laboratory parameters between the patients who died and who survived.

Imaging

Additional imaging methods may be used in the diagnosis of AMI, since it lacks specific clinical or laboratory findings. Angiography is the gold standard in the diagnosis of AMI (10). However, since it is unavailable in every center and is time consuming, its essentiality has become debatable. Preoperative angiography was not used for any of the patients in this present series, as it is not available in this center.

With a sensitivity and specificity rate of 0.96 and 0.94, respectively, CT angiography is a less invasive method that takes less time and currently it has also become the gold standard in the diagnosis of mesenteric ischemia. In this present study, CT angiography was used as an additional imaging method in 26 of the patients (50%) (11, 12).

Treatment

The importance of early diagnosis in the treatment of AMI has been repeatedly emphasized in many studies. Fluid resuscitation, invasive hemodynamic monitoring, prophylactic antibiotherapy, systemic anticoagulation, resection of ischemic and necrotic intestinal loops, restoration of blood supply, consideration of short bowel syndrome in terms of remaining intestine length, and critical intensive care are all essential components of treatment (14). The operative technique performed is directly related to the affected intestinal loop, and the extent of involvement has been reported to effect mortality. Extensive resections, the intense microbiological flora of the colon, bacterial translocation and its systemic effects have all been identified as causes of high mortality (19, 38).

The choice of the operative technique to be performed in our study was left to the surgeon, who decided on the operation according to the viability of the intestines. Viability of the intestine was defined according to the color of the intestinal segment, arterial pulsation and peristaltism. Six patients (13%) who had not undergone resection due to anextensive area of necrosis in both the small and large bowel died during the postoperative period. Seventeen patients (36.9%) in whom only small bowel ischemia was detected underwent resection and anastomosis, and 23 patients (50%) underwent resection and stoma creation. Second look operations were performed in 12 (26%) patients in the first 12-48 hours following the operation and re-resections were performed in four patients (8.6%). One patient (2.1%) underwent revascularization. One patient died in the early postoperative period. Mortality statistics for patients who had anastomosis following resection were found to be significantly low. We consider that this present study was accomplished with such a result due to the creation of a stoma was selected for patients who were in a worse general condition with a dirty intraabdominal cavity and a large ischemic area, and since the clinical course of such patients was more life-threatening.

In the literature, it is reported that mortality rates are higher in cases with colonic ischemia along with that of the small bowel. However, the presence of colonic involvement in addition to the small bowel had no statistically significant effect on mortality in this present study (26, 30).

Postoperative Period

The duration of postoperative intensive care and hospital stay did not significantly effectmortality (p=0.069 and p=0.146, respectively). Statistically, the rate of mortality was found to be significantly higher in patients who developed a wound site infection and sepsis (p=0.034 and p=0.007, respectively).

CONCLUSION

Suspicion of disease and early use of imaging (CT angiography) in addition to clinical and laboratory evaluations are essential in order to decrease mortality rates in AMI. Prevention of complications with critical intensive care during the postoperative period aids in decreasing the mortality rate. In addition, using the Mannheim Peritonitis Index can be helpful.

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

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

Peer-review: Externally peer-reviewed.

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

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

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

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Turk J Surg 2017; 33: 110-112
DOI: 10.5152/UCD.2015.2962

Case Report

Isolated thyroid metastasis from renal cell carcinoma

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ABSTRACT

Metastatic neoplasms of the thyroid are uncommon when compared to primary tumors of the gland. Renal cell carcinoma (RCC) is a highly aggressive tumor of the urinary system. It can spread all over the body. Isolated solitary metastases of RCC to the thyroid are very rarely observed. A 64-year-old woman with a history of left radical nephrectomy for RCC, was referred to our clinic with palpable thyroid nodule. Ultrasound confirmed the nodule on the left lobe. Histopathological examination of the thyroidectomy specimen revealed that there were two solitary metastasis of RCC. No other distant metastasis were detected. Metastatic tumors of the thyroid gland are very rare. When patients with thyroid nodule are referred to our clinic with the history of other malignancies, we must consider metastasis. Thyroidectomy is recommended in the case of isolated thyroid metastasis of RCC.

Keywords: Renal cell carcinoma, metastasis, thyroidectomy

INTRODUCTION

Renal cell carcinomas (RCC), (also known as renal adenocarcinoma) are most common cancer type of kidneys originating from proximal tubules. It accounts for 2–3% of all adult malignancies and is also the seventh most common cancer in men and the ninth most common cancer in women (1). Renal cell carcinoma can metastasize to all organs hematogenously. In 30% of the cases, metastasis is present at diagnosis (2). The most common sites of metastasis are lungs, bone, lymph nodes, and liver (3). Gastric, brain, and skin involvement are also rarely seen. Although the thyroid gland is the second most common vascular organ of the body following the adrenal glands, metastasis of RCC is seen very rarely. In the autopsy series, tumors that metastasize to the thyroid are generally lung, breast, kidney, and head and neck (4). Isolated thyroid metastasis of RCC is very rare. When present, metastatic RCC mimics primary tumors of the thyroid gland. Renal cell carcinoma generally presents as a mass in the neck.

We describe herein a patient with solitary metastasis to the thyroid, who had undergone a left nephrectomy for RCC 17 months previously.

CASE PRESENTATION

A 64-year-old woman with a history of 15 years of non-toxic multinodular goitre was consulted to our clinic from urology. She had no other symptoms such as dysphagia or dyspnea. A physical examination revealed palpable nodules on both sites of the thyroid gland. She had a left nephrectomy operation 17 months earlier. She was followed-up without any other treatment. On follow-up, thoracoabdominal computed tomography (CT) showed enlargement of the thyroid gland and hypoechoic nodule with a diameter of 22 mm in the left lobe of the thyroid gland (Figure 1). Ultrasound was performed on this neck. There was heterogeneity of the gland and there was a 22 mm hypoechoic nodule in the left lobe. The result of the radiological features and the thyroid volume led us to operate the patient. She did not accept the fine needle aspiration cytology.

A total thyroidectomy was performed in our clinic. Parathyroid glands and recurrent nerves were recognized and preserved. Macroscopic examination of the specimen showed that there is a 2 cm and 0.5 cm nodule and an ill-defined 0.8 cm nodule on the left lobe. The right lobe was normal. Microscopic examination revealed that there is lymphocytic thyroiditis and nodular hyperplasia in the nodule that is 2 cm in diameter, but there are some atypical cells with clear cytoplasm and large vesicular nuclei and prominent nucleoli in the nodules (0.5 cm diameter). The same atypical cells were also found in an area of 0.8 cm in diameter, in the same lobe out of the nodules described. We learned from the history of the patient that she had left nephrectomy 16 months ago for pT3 RCC. Immunohistochemical examination showed strong immunoreactivity with RCC and CD10 and

Cite this paper as:
Solmaz A, Muhammedoğlu A, Altınay S, Erçetin C, Yavuz E, Gülçiçek OB, Yalçın Ş, Erbil Y. Isolated thyroid metastasis from renal cell carcinoma. Turk J Surg 2017; 33(2): 110-112

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Received: 28.10.2014
Accepted: 27.11.2014
Available Online Date: 06.07.2015

vimentin. These neoplastic cells were negative for thyroid transcription factor-1 (TTF-1). These findings proved that these two nodules, which are 0.8 and 0.5 in diameter, are the metastasis of RCC (Figure 2). After the operation, the patient was referred to the oncology clinic.

DISCUSSION

Tumors of thyroid glands are mostly primary tumors, which are papillary, follicular, medullary, and anaplastic carcinomas in the order of frequency. On the other hand, metastatic thyroid gland tumors are seen very rarely and account for 2–3% of the thyroid malignancies (5). Common primary tumors metastasizing to the thyroid are lung, breast, kidney, and head and neck (4). These secondary thyroid gland tumors are found in 5–24% of the autopsy series. Metastases to thyroid in these autopsy series are generally multifocal, but in clinical series, metastases are solitary and <15 mm in size (6). Our patient displays similarities with literature in terms of the tumor diameter.

According to the article published by Chung et al. (7), the most common non-thyroid malignancies metastasizing to the thyroid are RCC (48.1%), colorectal (10.4%), lung (8.3%), breast carcinoma (7.8%), and sarcoma (4.0%). Metastases are generally nodular (44.2%) and are more common in females as observed in our case.

Renal cell carcinoma is the most common and very aggressive tumor of the urinary system. Its incidence increases with age. Until the widespread use of screening tests in recent years, many of the detected RCC had been metastasized. However, nowadays, by the use of these screening tests, 70% of them are detected as an incidental finding (8). This induces early detection of the cancer. However, despite early detection and surgical treatment, patients do not recover from the disease. We can see the metastasis of RCC even 10–20 years after diagnosis. Distant metastasis may be seen in one out of three patients. Our patient had left nephrectomy 16 months ago for pT3 RCC.

Renal cell carcinoma spreads hematogenously or through the lymphatic pathway to distant organs. The metastatic pathway is unpredictable for RCC. The lung, bone, liver, adrenal glands, brain, and skin are the most common sites of metastasis (8). The less frequent distant metastatic sites are orbit, parotid gland, nasal and paranasal cavities, tongue and tonsils, heart, skin, ovaries, uterus, testis, and thyroid glands.

The clinical findings of the primary and metastatic cancers of the thyroid gland are similar. We may not be able to differentiate them even with radiological evidences. Sometimes, fine needle aspiration biopsy may not be helpful in differentiating primary tumor from metastasis. However, if the pathologist is aware of the oncologic history of the patient, then by the use different antibodies and immunohistochemical studies, he/she may discriminate the pathology (9).

Thyroidectomy is recommended for isolated solitary thyroid metastasis of RCC. The mean survival rate after surgery is variable in the literature because the information about survival is limited to case reports. Heffess et al. (9) reported a series of 36 cases. According to this series, the mean overall survival period was 12.3 years from nephrectomy and 6.4 year from the date of thyroid metastasis. Machens and Dralle (10) reported that after definitive surgery of the thyroid metastasis of RCC, the mean survival rate may rise up to 30–60%. Considering that our patient, who was at an advanced age and presented with two nodules at a diameter of 5 mm and 8 mm, would have a poor prognosis, we are monitoring her closely in order to share her survival data in future studies.

CONCLUSION

Renal cell carcinoma can metastasize to distant organs even after many years. The thyroid gland is rarely affected by this. When the patient referred to our clinic with the thyroid nodule, we had data about the oncological history of the patient. If the patient had isolated thyroid metastases from RCC, thyroidectomy must be performed to improve prognosis.

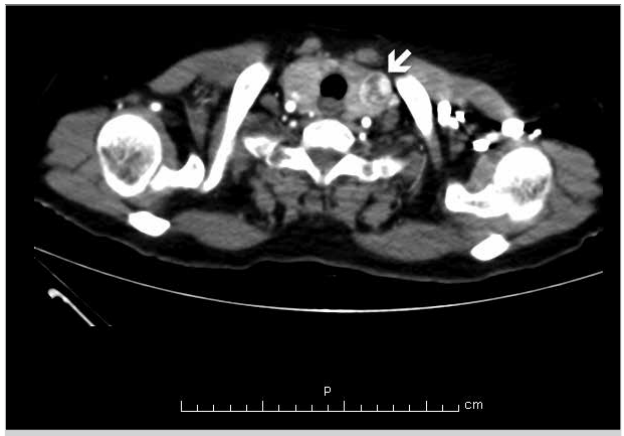

Figure 1. Axial computed tomography image of the neck: the white arrow indicates a mass of size 2.2 cm in the left lobe of the thyroid gland

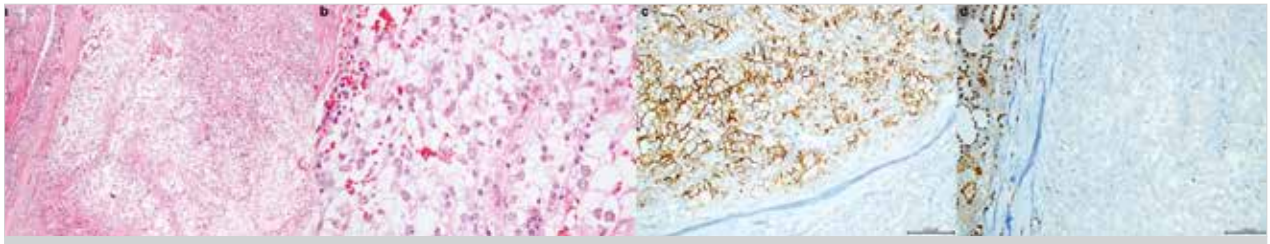

Figure 2. a-d. (a) The tumor area with clear cell morphology in the thyroid gland (×100; H & E). (b) High power illustration (×400; H & E). Differing from the surrounding thyroid tissue, the tumor tissue showed strong immunoreactivity with CD 10 antibody (c ×200), but negative with TTF-1 antibody (d ×200)

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.S., S.A.; Design - A.S., O.B.G., S.A.; Supervision - Y.E.; Funding - C.E., A.S.; Materials - A.M., S.A., Ş.Y.; Data Collection and/or Processing - E.Y., A.S.; Analysis and/or Interpretation - A.S., O.B.G., C.E.; Literature Review - E.Y., A.S.; Writer - A.S.; Critical Review - Y.E.; Other - A.S., O.B.G., S.A.

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

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

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Turk J Surg 2017; 33: 113-115
DOI: 10.5152/UCD.2015.2950

Case Report

The effect of corticosteroid treatment on bilateral idiopathic granulomatous mastitis

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ABSTRACT

Idiopathic granulomatous mastitis (IGM) is the commonly encountered form of granulomatous mastitis that may result into repetitive infections and/or abscess formation. Mastitis may develop secondary to a systemic disorder such as tuberculosis, diabetes mellitus, or rheumatoid arthritis, or it may develop as an idiopathic disorder. Idiopathic granulomatous mastitis is the most frequent form of all granulomatous diseases affecting the breast. This disorder frequently presents as painful and fast-growing mass in the breast. Biopsy is required to confirm diagnosis. Surgical excision and immunosuppressive treatment with corticosteroids are employed for therapeutic management. Here we present 3 female cases of bilateral IGM who were followed up and treated successfully with 1 mg/kg/day prednisolone.

Keywords: Idiopathic granulomatous mastitis, bilateral breast, corticosteroid treatment

Cite this paper as:
Çiftci F, Abdurrahman İ, Tatar Z. The effect of corticosteroid treatment on bilateral idiopathic granulomatous mastitis.Turk J Surg 2017; 33(2): 113-115

This study was presented as an e-poster in the 19th National Surgery Congress of Turkey held between 16-20th April, 2014.

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Received: 31.10.2014
Accepted: 15.12.2014
Available Online Date: 06.07.2015

INTRODUCTION

Mastitis is defined as the inflammation of the breast. The inflammatory process may sometimes be infectious. Mastitis affects women the most, particularly those who are middle aged. Idiopathic granulomatous mastitis (IGM) that mimics malignancy is a type of mastitis that has a chronic progression. Idiopathic granulomatous mastitis is a rare, chronic inflammatory disorder of which the etiology is not well known. It mimics breast cancer clinically and radiologically. It was first described in 1972 by Kessler and Wolloch (1) as noncaseating granulomatous inflammation in histopathological evaluation after ruling out infectious causes (such as tuberculosis and fungal infections) and noninfectious causes (such as sarcoidosis and vasculitis). Clinical presentation may be painful or painless palpable mass or skin fistula with retractions, thereby mimicking breast cancer (2). The disorder mimics breast cancer also in the ultrasonographic and mammographic evaluations (3). This study included three cases of IGM affecting bilateral breasts. The etiopathogenesis of IGM has been postulated to be a local autoimmune reaction or a secondary reaction to parturition, generally affecting young women unilaterally (4). Here we present three cases of granulomatous disease that were treated medically.

CASE PRESENTATIONS

Case 1

A 39-year-old woman who had previously given birth three times complained of redness of the skin, which she first noticed on the skin over the right and later on the left breast, along with pain and a palpable mass. She had a past history of excision of fibroadenoma from the upper lateral quadrant of her breast. The last time she gave birth was 5 years previously. She did not use oral contraceptives. On examination, we found hyperemia of indefinite margins on the skin over the medical parts of both areolas and an immobile palpable mass of 3×2 cm in the right breast and another of 4×3 cm in the left breast. White blood cell (WBC) count was 11.000 cells/mm^3. The masses were tender and hard. There was no nipple discharge, fistula orifice, or axillary lymphadenopathy. Prediagnosis was mastitis and oral sefuroxime axetil 500 mg twice daily was prescribed empirically along with diclofenac sodium. Bilateral breast ultrasonography showed lesions of heterogeneous low density, of which the contours were lobulated and poorly demarcated. There were no fluid collections and bilateral mammography was unremarkable. On pathological evaluation of excisional biopsies from both breast, IGM was diagnosed. The patient developed a continuing discharge from the incision wound of the left breast. Steroid treatment was continued along with weekly examinations. Tapering of steroid treatment depended on weekly clinical findings. She responded clinically well to a 6-week steroid (1 mg/kg/day) regimen. Follow-up period was 24 months. There were no complications or recurrence.

Case 2

A 31-year-old nulliparous woman who had been taking antidepressant drugs applied to the hospital complaining of redness of the skin over both breasts along with pain and swelling originating from the deeper regions of the breasts and spreading up to the retroareolar regions (Figure 1). WBC count was 9800 cells/mm^3. Ultrasonographic diagnosis was mastitis with bilateral retroareolar abscesses that were drained and biopsies were obtained. Steroid treatment was continued along with weekly examinations. Tapering of steroid treatment depended on weekly clinical findings. On pathological evaluation, IGM was diagnosed, and she was administered a 6-week course of steroid (1 mg/kg/day) therapy. Follow-up period was 18 months. There were no complications or recurrence.

Case 3

A 35-year-old woman who had previously given birth twice reported the use of oral contraceptives for 1 year and presented with multiple abscesses in both breasts. The abscesses were drained and from beneath the fistula tract tru-cut biopsies were obtained from the lesion. WBC count was 11800 cells/mm^3. Ultrasonographic diagnosis was multiple right breast masses with irregular margins and a highly hypoechoic echostructure with an irregular hyperechoic halo. Histopathological examination showed large nonnecrotic granulomas composed of numerous neutrophils, histiocytes, plasma cells, lymphocytes, and Langerhans-type giant cells. We perceived that granulomatous inflammation rendered the ducts to rupture. Idiopathic granulomatous mastitis was thus diagnosed histopathologically (Figure 2, 3). Steroid treatment was continued along with weekly examinations. Tapering of steroid treatment depended on weekly clinical findings. The patient responded well to a 10-week course of steroid (1 mg/kg/day) therapy. In the sixth week of follow-up, the patient developed dyspeptic complaints and proton pump inhibitor treatment was administered. Follow-up period was 20 months. There were no complications or recurrence.

Written informed consent was obtained from all patients who participated.

Figure 1. A case with bilateral mastitis: Arrows show external opening

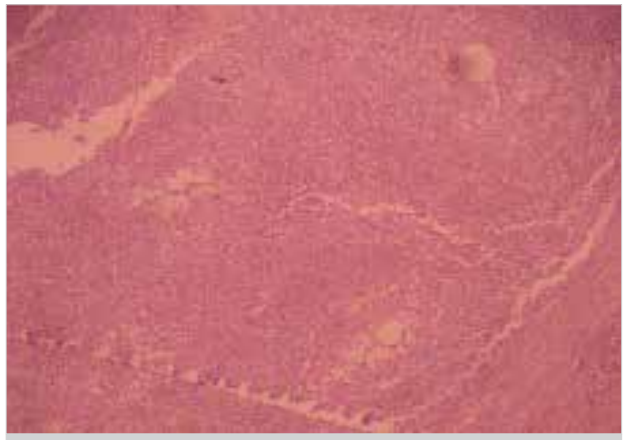

Figure 2. Histopathological features: At a smaller magnification, area depicting three separate small noncaseating granuloma structures can be observed

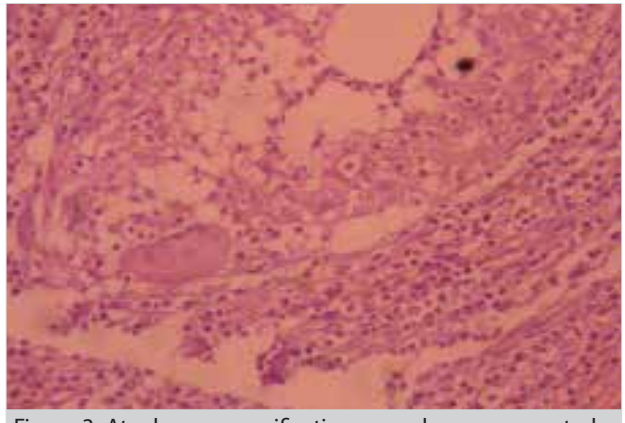

Figure 3. At a larger magnification, granulomas appear to be composed of the epitheloid histiocytes and multinuclear giant cells

DISCUSSION

As a rare chronic inflammatory disorder of the breast that may be confused with carcinoma IGM more frequently affects women of the middle age (the third and fourth decades) and is generally encountered within few years of parturition (5). The etiopathogenesis is not well known. Proposed predisposing factors include autoimmunity, oral contraceptive use, infectious agents, tuberculosis, hormonal disorders, pregnancy, hyperprolactinemia, and alpha-1 antitrypsin deficiency (6, 7). The higher incidence of IGM during the postpartum and lactation periods and that among women using oral contraceptives draws attention to hormonal factors. Approximately one-third (33%) of all IGM patients have reported the use of oral contraceptives and cases not related to pregnancy (8, 9). One of our cases reported a history of use of oral contraceptives. Histopathological findings including inflammatory cells in a lobular pattern suggest cellular autoimmune reaction against some histological elements of the breasts. Some cases have been reported to be affected by other autoimmune disorders (10). However, in contrast to other autoimmune disorders, the absence of vasculitis or prominant plasma cell infiltration disfavors the possibility of autoimmune reaction. Thus far, no microorganism has been isolated from the lesions, thus ruling out infectious factors.

In addition to mimicking breast carcinoma, other diseases that may cause a granuloma in the breast, such as tuberculosis, syphilis, histoplasmosis infections, foreign-body granuloma, vaccination granuloma, mammary duct ectasia, sarcoidosis, Wegener's granulomatosis, giant cell arteritis, and polyarteritis nodosa, should also be excluded. Here we reported three

cases of IGM successfully treated with 40 mg/day (1 mg/kg/day) prednisolone. Because steroid administration can cause some severe adverse effects, such as opportunistic infections, dermatological manifestations, hypertension, peptic ulcer disease, neuropsychiatric symptoms, hyperglycemia, myopathy, and osteoporosis, we believe that the minimum dosage of a steroid should be recommended. The duration and recommended dosage of steroid treatment require further clinical research to establish an adequate treatment regimen. Several other reports of using 60 mg/kg/day prednisolone to treat IGM have also been published. However, in the literature the recommended dose ranges between 0.5 and 2 mg/kg/day (11-15).

One of our cases had the history of use of oral contraceptives before and after parturition. She had no diagnosis for other autoimmunities and the histopathological evaluation did not show vasculitis. Sarcoidosis is a granulomatous disorder of unknown cause. The granulomas in sarcoidosis are discrete and perivascular and include no necrosis or microabscesses. In our cases, there were no radiological findings attributable to sarcoidosis, and the presence of microabscesses on histological examination rules out sarcoidosis.

Idiopathic granulomatous mastitis affects both breasts at the same frequency and can be bilateral in 5%–15% of cases. Involvement of upper lateral quadrant is most commonly reported (2, 10, 14). Our study included bilateral cases of granulomatous mastitis. Clinical presentation of the disorder is mostly painful or painless palpable mass in the breast. It may present as acute inflammation with erythema, tenderness, and warmth or may exhibit a chronic progression with fistula, abscesses, and ulceration of the skin over the breast, retraction and leaks from the nipple thereby mimicking breast cancer (11). Although very rare, axillary lymph nodes may be palpable.

CONCLUSION

This study included three cases of IGM affecting bilateral breasts. Here we described the clinical presentation, diagnosis, evaluation, and treatment of this disorder. Its clinical presentation may mimic breast cancer or abscess.

Thus far, no consensus regarding the treatment modality has been reached. Current studies suggest preventing aggressive intervention as the initial approach in cases of IGM with minimal clinical findings. However, surgery is unavoidable in cases that do not respond to medical treatment or present with grave clinical findings (such as recurrent abscesses and fistula).

Nonoperative approaches and medical treatment with steroids are preferred for patients with bilateral IGM.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Ç.; Design - F.Ç.; Supervision - F.Ç.; Funding - F.Ç.; Materials - F.Ç.; Data Collection and/or Processing - F.Ç., Z.T.; Analysis and/or Interpretation - F.Ç., I.A.; Literature Review - F.Ç., Z.T.; Writer - F.Ç., I.A.; Critical Review - F.Ç., I.A., Z.T.

Acknowledgements: The authors express their gratitude and thanks to all participating patients and clinical staff.

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

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

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Turk J Surg 2017; 33: 116-118
DOI: 10.5152/UCD.2015.2983

Case Report

Extra-adrenal myelolipoma with hemolytic anemia

Nidal İflazoğlu[1], Orhan Üreyen[2], Mahir Keleş[3]

ABSTRACT

Myelolipomas are rare benign tumors often detected as adrenal masses. Extra-adrenal myelolipomas are encountered even more rarely. The rate of detection of these lesions is increasing with improved radiological techniques. Because of their localization and morphological similarities to well differentiated liposarcomas, extra-adrenal myelolipomas need to be differentiated from other aggressive neoplasms. Preoperative imaging and percutaneous biopsy are important tools in the diagnosis of these lesions. We report a very rare case of an extra-adrenal perirenal myelolipoma associated with hemolytic anemia. The etiology, differential diagnosis, and treatment options for the lesion have been discussed. Fat-containing tumors of the retroperitoneum should be considered in the differential diagnosis. Accurate diagnosis is important to avoid over-treatment of these benign lesions.

Keywords: Myelolipoma, anemia, hemolytic

INTRODUCTION

Myelolipomas are small, asymptomatic, infrequently encountered lesions of the adrenal cortex (1). They frequently contain mature adipose tissue and hematopoietic elements (both myeloid and erythroid) (2). Extra-adrenal myelolipomas are rarer, with about 100 cases reported in the literature most of which are associated with different lesions and encountered in diverse localizations (2). The incidence of myelolipomas in the autopsy series is less than 1% (3). To the extent of our knowledge, no case of extra-adrenal myelolipoma with accompanying hemolytic anemia has been reported. The known localizations are the presacral soft tissue, retroperitoneum, pelvis, stomach, and rarely the perirenal tissue (4-7). The prognosis is very good and no malignant degeneration has been reported (8). The histological appearance of extra-adrenal myelolipomas is identical to that of well-differentiated liposarcomas. Therefore, retroperitoneal tumors with fat content should always be kept in mind during the differential diagnosis.

CASE PRESENTATION

A 26-year-old woman presented to our hospital with abdominal pain and malaise. There was no significant knowledge of her medical and familial history. Abdominal ultrasonography and abdominal computerized tomography (CT) revealed an 8 cm perirenal mass, not related to the adrenal gland (Figure 1a, b). Her laboratory values showed anemia with iron and vitamin B12 deficiency [Hemoglobin: 6.2 gr/dL, N: 12.2–18.1 gr/dL; mean corpuscular volume: 81.1, N: 80–96; and the red cell distribution width: 14.4, N: 11.8–15.6]. The white blood cell and platelet counts were within normal ranges. Detailed laboratory tests were performed and elevated C-reactive protein and ferritin values, as well as indirect Coombs' test positivity, and normal liver and kidney function tests were determined. To exclude an infectious etiology, blood and urine cultures and tube agglutination tests for brucella and salmonella were performed, all of which turned out to be negative. The tumor markers (CA 125, CA 19-9, CEA) were within the normal range. Following the hospitalization of the patient, the daily complete blood count analyses showed a gradual decrease in the hemoglobin levels to 3.8 g/dL. Empirical antibiotic treatment (ceftriaxone 2 g and metronidazole 1.5 g daily) was initiated. The peripheral blood smear of the patient was compatible with partial hemolysis. Bone marrow aspiration and smear and other laboratory tests were performed and were found to be compatible with hemolytic anemia. Intravenous prednisolone was initiated and blood replacement was performed. Under oral deltacortril treatment (10 mg/day), her hematological parameters had a stable course. We decided to perform laparotomy because of a symptomatic (pain and hemolytic anemia) mass in the abdomen. Before the operation, we placed a double J stent in the right ureter. Conventional surgery was performed. In the right perirenal area, we observed a mass 8 cm in diameter encircling the right ureter. The ureter's wall was observed to be very thin. The mass was excised totally with conservation of the right ureter, kidney, and adrenal glands. After the surgery, the deltacortril dose was gradually reduced and then stopped on the 20th day. The patient was discharged and followed-up in the out-patient clinic and her consent for publication was taken. Her hematological parameters were observed to be stable.

Cite this paper as:
İflazoğlu N, Üreyen O, Keleş M. Extra-adrenal myelolipoma with hemolytic anemia. Turk J Surg 2017; 33(2): 116-118

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Received: 08.11.2014
Accepted: 21.12.2014
Available Online Date: 06.07.2015

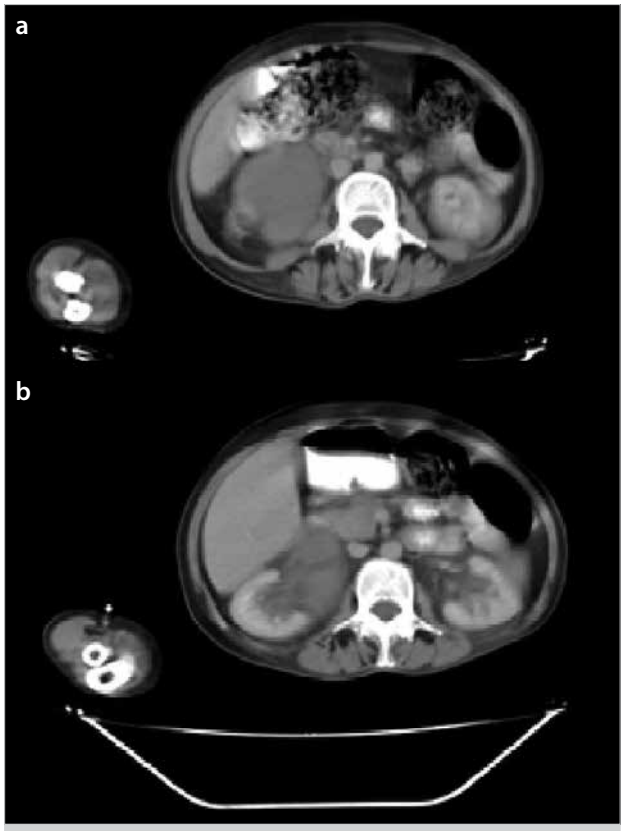

Figure 1. a, b. (a) Perirenal mass, computerized tomography. (b) Perirenal mass, computerized tomography

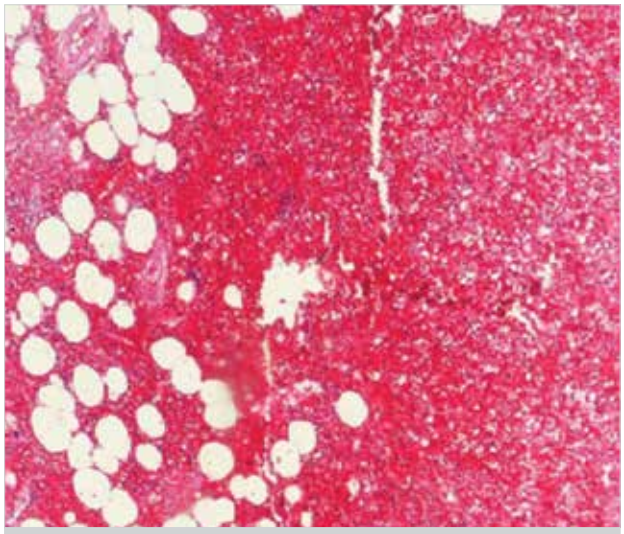
Figure 2. Fat and myeloid cells, hematoxylin–eosin, ×100

The excised mass was evaluated histopathologically. A 8 × 6 × 6 cm mass having an intact capsule and external appearance that was partly yellow and partly brown was observed. Dispersed among the fat cells were non-uniform hematopoietic areas containing granulocytic, erythrocytic, and megakaryocytic elements (Figure 2). In the light of the pathological findings, the mass was diagnosed to be a myelolipoma.

DISCUSSION

Myelolipomas are rare benign tumors of mature hematopoietic tissue and fat and tumorigenic processes are poorly understood. They most commonly occur in the adrenal glands, but extra-adrenal myelolipomas have been reported in other locations such as the presacral region or retroperitoneum (4-7). It is not unusual that they are incidental findings revealed during the evaluation for different diseases (9). Although there are several theories regarding their etiology, the process is not yet fully understood. One of the theories proposing these tumors is the result of the differentiation of ectopic adrenal or hematopoietic cells in response to a triggering stimulus (10), whereas another theory by Chang et al. (11) suggests that myelolipomas are formed as a result of translocation t(3;21)(q25;p11). Bishop et al. (12) demonstrated chromosome X inactivation in the fat and hematopoietic cells and proposed a clonal origin for myelolipomas.

Extra-adrenal myelolipomas are observed frequently over the age of 40 with a female predominance. Their diameters are on average about 8 cm, although their size can vary between 4 cm and 15 cm (13), with cases having been reported of being up to 27 cm in size (10). Despite our patient being younger, her sex and tumor size were in accordance with the literature. Extra-adrenal localization can be in any part of the body, but the presacral area and more rarely the retroperitoneum are the most common sites reported, whereas only a few cases have been reported in the perirenal area (2, 10). They are usually incidental findings because they are mainly asymptomatic; only in 10% of cases, depending on the size and site of the lesion, they are observed to be symptomatic due to the compression of local structures (2). Hemorrhage in extra-adrenal myelolipomas is a very rare complication, and no case has been reported in the literature, which caused the clinical findings of acute hemorrhage. Myelolipomas are hormonally inactive, but about 10% are associated with several endocrine disorders such as Cushing's syndrome, congenital adrenal hyperplasia, Conn's syndrome, pheochromocytoma, hyperparathyroidism, or adrenogenital syndrome (2). Our case was diagnosed as a result of evaluation for abdominal pain and serious anemia, and had no other accompanying disorders, endocrinological or otherwise. Hemolytic anemias caused by thalassemia major, thalassemia intermedia, sickle cell anemia, and hereditary spherocytosis have been reported in cases of large adrenal myelolipomas (14, 15), but no case of hemolytic anemia in extra-adrenal myelolipomas have been defined in the literature.

A common consensus on the surgical approach to myelolipomas has not yet been reached due to the limited number of extra-adrenal myelolipoma cases and the literature has thus been limited to case reports. Commonly, surgical excision is performed because of the symptoms that are caused by mass effect and due to the fact that the nature of the tumor is unknown (2). Adrenal myelolipomas can usually be diagnosed radiologically, but such is not the case with extra-adrenal myelolipomas due to a lower fat content and rarity of the lesion. In such cases, percutaneous fine needle biopsy can be performed in a simple, safe, and efficient manner (2). Because the mass in our case was symptomatic and sufficiently large, the patient was operated rather than biopsied. Microscopically, extramedullary hematopoietic tumors have a predominance of hematopoietic elements, with erythroid hyperplasia. Fat is not an enlarged component of the process (13). Extra-adrenal myelolipomas may have a predominance of either the hematopoietic or fatty component, usually the latter, and generally have a more conspicuous lymphocyte population (10).

Despite the fact that the presence of hematopoietic cells (myeloid, erythroid, and megakaryocytic) and mature adipose tissue of varying amounts are used for the diagnosis, the observation of megacaryocytes forms the basis of the diagnosis of extra-adrenal myelolipoma (2, 13). Our case demonstrated all three types of the hematopoietic cells as explained above.

CONCLUSION

Consequently, today, it is possible to reach a definitive diagnosis using advanced radiological techniques and percutaneous biopsy; therefore, the number of unnecessary laparotomies and the emotional and economic burden on the patient and the society can be reduced. It must be kept in mind that myelolipomas can, though rarely, cause severe hemolytic anemia and can be located in an extra-adrenal site, and in any part of the body.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.İ., M.K.; Design - N.İ., O.Ü.; Supervision - N.İ.; Analysis and/or Interpretation - O.Ü., M.K.; Literature Review - N.İ.; Writer - N.İ., M.K.; Critical Review - O.Ü.

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

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

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Turk J Surg 2017; 33: 119-122
DOI: 10.5152/UCD.2015.2925

Case Report

Isolated chylous injury due to blunt abdominal trauma: Report of a case and a review of the literature

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ABSTRACT

The chyle duct (CD) lies close to the spine behind the right renal vein and vena cava. Forces capable of tearing the CD may also injure other adjacent structures or organs. Cases of isolated chylous injury are rarely reported in the literature. Our aim was to report a case of isolated chylous injury due to blunt abdominal trauma that was successfully treated non-operatively. A 54-year-old man was involved in a deceleration-type traffic accident. His physical examinations, radiologic evaluations, paracentesis, and laboratory findings revealed isolated chylous injury resulting from intra- and retroperitoneal chylous fluid collection. The patient was treated via percutaneous drainage and medical therapy. This condition is generally self-limited and resolves without the necessity of any surgical interventions. However, if medical treatment is unsuccessful, the decision of diagnostic laparoscopy or exploratory laparotomy becomes inevitable.

Keywords: Abdominal trauma, chylous ascites, chyloretroperitoneum

INTRODUCTION

The cisterna chyli is an important structure because it receives the lymphatic drainage from the intestinal trunk, the right and left lumbar lymphatic trunks, and small lymph vessels that descend from the lower part of the thorax. Injury to the cisterna chyli is rare and eventful. It may manifest with chylous ascites and chyloretroperitoneum (1, 2).

Chylous ascites is the accumulation of a milk-like peritoneal fluid that is rich in triglycerides, due to the presence of thoracic or intestinal lymph in the abdominal cavity. It develops when there is a disruption of the lymphatic system due to traumatic injury or obstruction (from benign or malignant causes) (3).

Many pathological conditions can result in chylous ascites. These conditions include congenital defects of the lymphatic system; nonspecific bacterial, parasitic, and tuberculous peritoneal infections; liver cirrhosis; malignant neoplasm; surgical injury; and blunt abdominal trauma. However, the most common cause in adults is believed to be abdominal malignancy, while congenital lymphatic abnormalities is the most common cause in the pediatric population. The incidence of chylous ascites seems to be increasing because of more aggressive thoracic and retroperitoneal surgeries and with the prolonged survival of patients with cancer (4). Examples for surgical procedures that may be associated with chylous ascites are abdominal aortic aneurysm repair, retroperitoneal lymph node dissection, pancreaticoduodenectomy, liver transplantation, catheter placement for peritoneal dialysis, distal splenorenal shunt, inferior vena cava resection, and laparoscopic Nissen fundoplication (3).

Progressive and painless abdominal distention is the major clinical manifestation of chylous ascites, which occurs over the course of weeks to months, depending upon the underlying cause. Acute onset of symptoms may be observed in patients who have undergone either an abdominal or thoracic surgical intervention or had a major traumatic injury.

Blunt abdominal trauma resulting in intestinal and mesenteric injury is also another important cause of chylous ascites (1). However, cases of chylous injury without any affected adjacent structure or organs after blunt abdominal trauma are rarely reported in the literature.

We herein report a case of isolated chylous rupture due to blunt abdominal trauma with manifestations of both chylous ascites and chyloretroperitoneum.

CASE PRESENTATION

A 54-year-old man was involved in a deceleration-type traffic accident when he was in the passenger seat of an automobile with his seat belt strapped on. The patient was admitted to our emergency department (ED) 3 days after the accident with complaints of abdominal pain, nausea, and vomiting. He had no systemic diseases, but his past history revealed a right hemicolectomy and adjuvant chemotherapy 16 years ago due to right-sided colon cancer.

Cite this paper as:
Eren T, Demir M, Orman S, Leblebici M, Özemir İA, Alimoğlu O. Isolated chylous injury due to blunt abdominal trauma: Report of a case and a review of the literature. Turk J Surg 2017; 33(2): 119-122

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Received: 25.09.2014
Accepted: 02.12.2014
Available Online Date: 06.07.2015

On physical examination, the patient was hemodynamically stable, and he had a painful abdominal distension at the epigastric region. Except for this finding, his abdomen was soft with very mild tenderness to palpation over the rest of the entire abdomen. There was no rebound tenderness. Bowel sounds were active. Digital rectal examination showed no abnormal findings. Blood urea nitrogen (BUN), electrolytes, and amylase levels were normal as well as his complete blood count. Abdominal X-ray findings were normal. In addition, other routine radiographs revealed no bony injuries. A signed informed consent was obtained from the patient, and he was hospitalized for further evaluation and treatment.

We performed an ultrasound scan to identify the epigastric distension of the abdomen. A major retroperitoneal fluid accumulation of 6 × 6 × 4 cm on the right side, inferior, and medially to the pancreas was demonstrated ultrasonographically, and free intraperitoneal fluid was also detected in the pelvic region. A pancreatico-duodenal injury was suspected according to these initial findings.

The patient underwent a contrast-enhanced computed tomography (CT) scan of his abdomen. The CT scan showed an irregular, extensive, hypodense retroperitoneal fluid collection with dimensions of 9 × 7 × 6 cm on the right side, inferior, and medially to the pancreas at the level of the second lumbar vertebra (Figure 1). In addition, there were small hypodense fluid collections in the Morrison's pouch, the perisplenic and perihepatic regions, and the rectovesical recess with a density similar to water (Figures 2, 3). However, no findings of any solid or luminal organ injuries were detected.

According to the radiological findings, a diagnostic paracentesis was performed which revealed a white-milky, odorless fluid with a density of 1.030. The findings revealed the following values: sodium, 139 mEq/L; potassium, 3.6 mEq/L; total protein, 3.4 g/dL; glucose, 96 mg/dL; amylase, 21 IU/L; lipase, 8 IU/L; triglycerides, 772 mg/dL; and cholesterol, 86 mg/dL. The concurrent standard blood tests were at normal levels. The Gram staining and bacterial cultures were found to be negative. As a result, the collected fluid was experimentally confirmed to have a chylous character.

The initial volume of the drainage was 600 mL at the time of paracentesis. A catheter was left in the abdominal cavity and the drainage continued with a flow of approximately 200 mL/day. The patient was treated non-operatively with intravenous fluids and analgesia. Total parenteral nutrition (TPN) and intravenous administration of somatostatin at a dose of 6 mg/day via an infusion pump was started the day after the intervention. On the third day, the volume of the drainage was 100 mL/day. Low-fat diet with a restriction of long-chain triglycerides was started on the fourth day.

With intensive treatment, the drainage steadily decreased and stopped by the 10th day. The abdomen was found to be normal on physical examination, and no signs of chylous ascites were found on ultrasonography images. The drainage tube was removed, and the patient was discharged on the 13th day uneventfully.

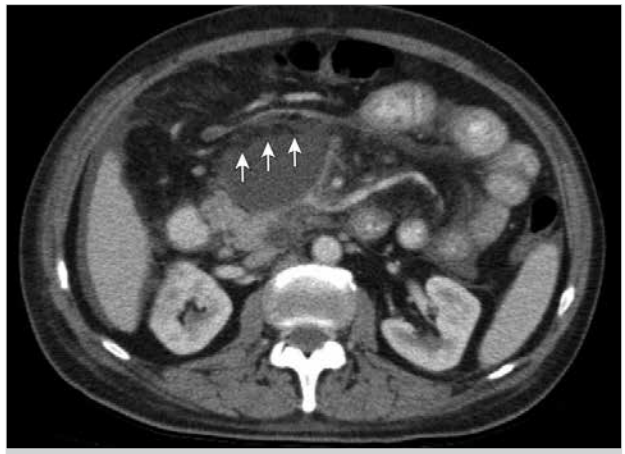

Figure 1. Computed tomography image of the irregular, extensive, hypodense retroperitoneal fluid collection, with dimensions of 9 × 7 × 6 cm also revealing a thin fat-fluid level marked by the arrows

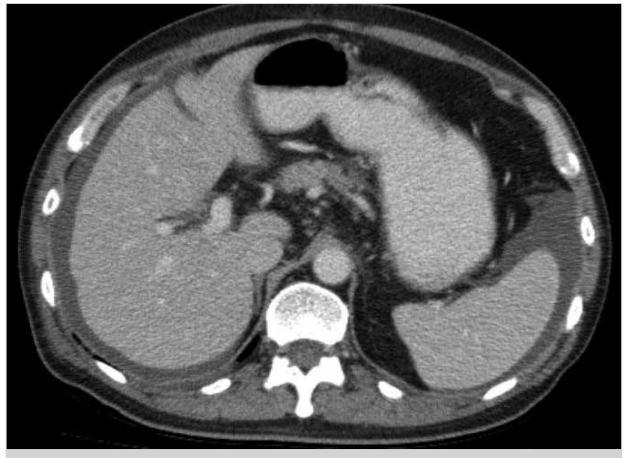

Figure 2. Computed tomography image of the small, hypodense fluid collections in the Morrison's pouch and the perisplenic and perihepatic regions

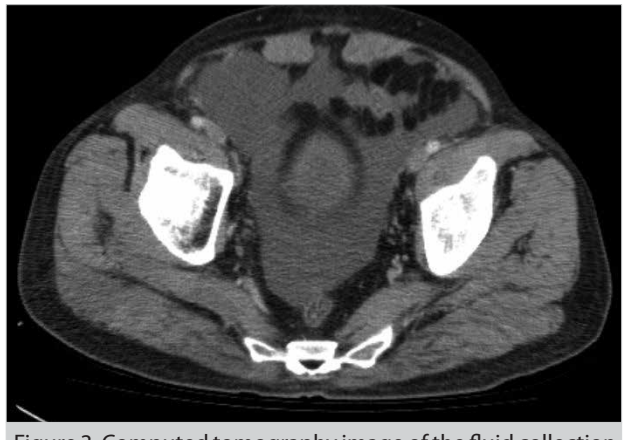

Figure 3. Computed tomography image of the fluid collection in the rectovesical recess

He was followed-up at office visits on the 15th and 30th days of the initial intervention, and a control examination was also scheduled for the third month of the event. He did not have any complaints in these short-term follow-ups, and no abnormal findings were detected on his physical examinations.

DISCUSSION

The lymphatic system is an accessory route by which fluids, proteins, and lipids can flow from the interstitial spaces to the vascular system. Almost all tissues of the body have lymphatic channels composed of one-way valves that drain the excess fluid from the interstitial spaces of tissues. Lymph from the lower part of the body drains into the thoracic duct. This duct arises from the cisterna chyli, which lies between the aorta and the inferior vena cava anterior to the bodies of the first and second lumbar vertebrae. The thoracic duct passes through the aortic hiatus of the diaphragm to enter the posterior mediastinum. It continues between the aorta and azygous vein until it reaches the fifth thoracic vertebrae. At this point, it crosses to the left to enter the superior mediastinum behind the aortic arch and empties into the venous system at the junction of the internal jugular vein and subclavian vein (3).

Chylous ascites is an uncommon finding with a reported incidence of approximately 1 in 20000 admissions at a large university-based hospital over a 20-year period (3). Traumatic chyloperitoneum is a rare injury. Forces capable of tearing the cisterna chyli or the thoracic duct will generally also injure other structures such as the liver, duodenum, kidney, and pancreas (5). As far as we could extract from the literature, up to 10 cases have been reported describing isolated traumatic chylous injury causing either intra- or retroperitoneal fluid collection. The patient that we herein report was a case with an isolated chylous rupture due to blunt abdominal trauma presenting with both chylous ascites and chyloretroperitoneum without any other concomitant organ injuries.

A detailed history should be obtained and a careful physical examination should be performed, similar to that in any patient presenting with acute onset ascites. The patient should be questioned regarding weight loss or gain, symptoms of malignancy, family history, underlying liver or kidney disease, travel, recent abdominal surgery, and abdominal trauma (3). In our patient, blunt abdominal trauma, which took place 3 days before his admission to our emergency service, was the cause of chylous ascites and chyloretroperitoneum.

Chylous leak after non-penetrating trauma, which constitutes the pathogenesis of traumatic chylous ascites, is generally attributed to hyperflexion-extension of the vertebral column with shearing of tethered lymphatics. Alternatively, sudden compression of the lipemic and engorged mesenteric lymphatics, adjacent nodes, and lower thoracic duct aggravated by deformations associated with stretching and tearing motions may also directly disrupt chyle containing lymphatics (6). The car accident of the deceleration type or the presence of the seat belt may have affected the vertebral column of our patient, and hyperextension followed by hyperflexion may be the reason of the chylous injury.

It is important to remember that chyle leaks slowly into the peritoneal cavity through lymphatic fistulas or by back-pressure on the intestinal lymphatics, and significant quantities of chylous ascites may take some time to accumulate (5). In our case, the patient emphasized that he was well until the second day after the accident. He remarked that all his symptoms started on the second day of the event after dinner when he had eaten fried lamb chops, which was a fatty meal.

Radiation therapy to the abdomen causes fibrosis and obstruction of the lymphatic vessels in the small bowel and mesentery (7). According to the surgical history of our patient, although there was an adjuvant chemotherapy anamnesis following right hemicolectomy due to right-sided colon cancer, he did not reveal a past history of any kind of radiation therapy.

There are several diagnostic modalities available. Particularly, CT scanning makes the diagnosis easier because it enables identifying pathologic intra-abdominal lymph nodes, masses, and solid and luminal organs, and it also helps in determining the extent and localization of the fluid. In chylous ascites and chyloretroperitoneum the CT reveals a collection of fluid with a similar density to water and ascites (5). If the patient lies in a supine position for an extended period, he may show a fat-fluid level, which is pathognomonic for this condition (8). When we performed the CT scan for our patient, we visualized the presence of an extensive hypodense retroperitoneal fluid collection, which contained a thin layer of patchy images of the intensity of floating fat, thus forming a fat-fluid level (Figure 1). In addition, there were small hypodense fluid collections in the Morrison's pouch, the perisplenic and perihepatic regions, and the rectovesical recess (Figure 2, 3). However, no other findings of any concomitant solid or luminal organ injuries were detected. We confirmed the diagnoses of both chylous ascites and chyloretroperitoneum based on the CT scan which guided our treatment approach.

Abdominal paracentesis is generally the most important diagnostic tool in evaluating and managing patients with ascites, and this issue is valid for chylous ascites as well. Typically, chyle has a cloudy and turbid appearance, in contrast to the straw-colored and transparent appearance of ascites caused by cirrhosis or portal hypertension. Ascitic fluid should be sent for the analysis of the cell count and culture; Gram staining; total protein concentration; albumin, glucose, LDH, amylase, and triglyceride levels; and cytology. The total protein content in chylous ascites varies depending on the underlying cause and ranges between 2.5 and 7.0 g/dL (3). The triglyceride levels in the ascitic fluid are critical in defining chylous ascites. Triglyceride values are typically found to be above 200 mg/dL, although some authors use a cut-off value of 110 mg/dL (9). We performed an abdominal paracentesis on our patient and obtained a white milky, odorless fluid with a density of 1.030. The findings revealed the following values: sodium, 139 mEq/L; potassium, 3.6 mEq/L; total protein, 3.4 g/dL; glucose, 96 mg/dL; amylase, 21 IU/L; lipase, 8 IU/L; and cholesterol, 86 mg/dL. The concurrent standard blood tests were at normal levels. The Gram staining and bacterial cultures were negative. The triglyceride level was 772 mg/dL in our case, which constituted the most valuable diagnostic parameter. At the same time, the color of the fluid, and the total protein, cholesterol, glucose, and amylase values were all proper for defining chylous ascites.

Lymphangiography is an imaging modality for investigating chyluria, chyloperitoneum, and chylothorax. It is useful for detecting abnormal retroperitoneal lymph nodes, leakage from dilated lymphatics, lymphoperitoneal and lymphaticopelvic fistulization, skipping of lymphatic chain, patency of thoracic duct, and abnormal leg lymphatics. However, it requires tedious cannulation of lymphatics. It can also result in local tis-

sue necrosis, fat embolism to the lungs, hypersensitivity reaction, and exacerbation of lymphedema by the contrast material (10). Lymphoscintigraphy can be performed to acquire information about the localization of the injury using ^{99m}Tc sulfurmicrocolloid, antimony sulfide colloid, stannous phytate, rhenium sulfur colloid, human serum albumin, or dextran. It delineates the pattern of lymphatic drainage, is fast and non-traumatic, and does not have major side-effects (6, 10). However, these tests are invasive and are often deferred until other modalities fail. Because we already succeeded in the diagnosis and treatment of our patient, there was no necessity to perform either lymphangiography or lymphoscintigraphy.

Somatostatin or octreotide have been used successfully to treat chylous effusions in patients with the yellow nail syndrome and lymphatic leakage due to abdominal and thoracic surgery (3). The exact mechanisms of somatostatin on drying lymphatic fistulas are not completely understood. It has been previously shown to decrease the intestinal absorption of fats, lower triglyceride concentration in the thoracic duct, and attenuate lymph flow in the major lymphatic channels. In addition, it also decreases gastric, pancreatic, and intestinal secretions; inhibits motor activity of the intestine; slows the process of intestinal absorption; and decreases splanchnic blood flow, which may further contribute to decreased lymph production. Total parenteral nutrition allows the bowel to rest and decreases the production and flow of the lymph. Somatostatin along with TPN can close the lymphatic leakage or relieve the symptoms effectively and rapidly compared with that of conventional regimens (4). We simultaneously started TPN and administered somatostatin at a dose of 6 mg/day via an infusion pump and observed that the drainage decreased by the second day of the treatment.

In cases of chylous injury, a high-protein and low-fat diet with medium-chain triglycerides (MCT) is the best dietary choice (4). Dietary restriction of long-chain triglycerides (LCT) avoids their conversion into monoglycerides and free fatty acids (FFA), which are transported as chylomicrons to the intestinal lymph ducts. In contrast, MCTs are absorbed directly into intestinal cells and transported as FFA and glycerol directly to the liver via the portal vein. Thus, a low-fat diet with MCT supplementation reduces the production and flow of the chyle (3). We preferred a low-fat diet with MCT for our patient as well, and the amount of chyle decreased dramatically.

In patients with chyloperitoneum, if ascites does not respond to conservative management in 2 weeks, surgical exploration should be performed (2). When surgical treatment is indicated, exploratory laparotomy necessitates a formal exploration to rule out any concomitant injuries of the intraabdominal organ or structures. The surgeon must carefully inspect the mesenterium, beneath the diaphragm, around the aorta and pancreas. Maurer et al. (1) reported that if the retroperitoneum is intact and retroperitoneal space is found to be bulging from the mesenteric root to the bifurcation of the aorta with a cream-like fluid collection without the presence of any chylous ascites intraoperatively, it is not recommended to open the retroperitoneum to avoid the formation of chylous ascites and to maintain the retroperitoneal compression. However, if chylous ascites and retroperitoneal rupture is present at laparotomy, the retroperitoneal space should be explored and the ruptured lymphatics must be ligated to stop chyle leakage. Patten et al. reported two cases of isolated traumatic chylous injury, both of whom were surgically treated via retroperitoneal dissection and the ligation of the ruptured cisterna chyli (5). Because the chyle drainage stopped by the 10th day, our patient was considered to be successfully treated non-operatively. Following his control imaging studies and examinations, the drainage tube was removed and he was discharged on the 13th day and was followed-up at office visits.

CONCLUSION

A detailed history and a thorough physical examination accompanied with appropriate imaging modalities and paracentesis are the most important points in the diagnosis and treatment of chylous injury due to blunt abdominal trauma. The condition is generally self-limited and resolves without the necessity of any surgical interventions. However, if the dietary management and medical treatment is unsuccessful, the decision of diagnostic laparoscopy or exploratory laparotomy becomes inevitable.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.E., M.D., O.A.; Design - T.E., M.D.; Supervision - O.A.; Materials - T.E., M.D., M.L.; Data Collection and/or Processing - T.E., M.D., S.O., M.L.; Analysis and/or Interpretation - T.E., İ.A.Ö., O.A.; Literature Review - T.E., M.D., S.O.; Writer - T.E., M.D.; Critical Review - T.E., O.A.; Other - S.O., İ.A.Ö.

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

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

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Turk J Surg 2017; 33: 123-125
DOI: 10.5152/UCD.2015.2920

Case Report

A rare cause of acute abdomen: Chylous ascites

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ABSTRACT

Chylous ascites, defined as a lipid-rich fluid accumulation in the peritoneal cavity, is a rare pathology of the lymphatic system and is a very rare cause of acute abdomen. It is generally associated with diseases such as cancer, cirrhosis, inflammatory diseases, surgery, or trauma. In this study, we report a patient with chylous ascites, which mimics acute appendicitis. Diagnosis and treatment procedures were discussed.

Keywords: Acute abdomen, appendectomy, chylous ascites

INTRODUCTION

Chylous ascites is the accumulation of lipid-rich fluid in the peritoneal cavity and was first described by Morton in 1691 (1). It usually occurs secondary to chronic disorders including lymphoma, various cancers, liver cirrhosis, and infectious diseases such as tuberculosis. Traumatic injuries to the lymphatic system are also found to be related to chylous ascites (2). Chylous ascites is responsible for 0.5% of all acid-making pathologies and less than 1% of all malignant ascites (3). Clinical findings are related to the ascites volume. Rapid accumulation of the fluid in the peritoneal cavity may lead to acute abdomen, whereas the same volume is well tolerated by patients who have chronic disorders.

CASE PRESENTATION

A 30-year-old male was admitted to the emergency department with abdominal pain, loss of appetite, nausea, and vomiting for the last two days. He had acute onset pain that was primarily felt at the epigastrium. There were no special features in his medical history. His overall health condition was not affected, showing a temperature of 38.4°C, heart rate at 100 beats per minute, and arterial pressure of 125/75 mm-Hg. On physical examination, bowel sounds were found to be hypoactive, and rebound tenderness was observed on the right lower abdominal quadrant. The rectal digital examination was unremarkable. The laboratory results showed only an elevated white blood cell count [14×10^6/L (normal range: 3.8×10^6–10.0×10^6 /L)]. Abdominal ultrasonography revealed an 8-mm diameter, blind-ending non-compressible intestinal segment with free intra-abdominal fluid. As the findings were thought to be suspicious for acute appendicitis, the patient was subsequently taken to the operating room. After the abdominal cavity was entered through McBurney's incision, approximately 600 cc of free "milky" fluid was discovered. The appendix was in the normal location but was hyperemic and edematous. Therefore, appendectomy was performed. Laparotomy was then performed for further evaluation, and an edematous area was observed within the small bowel mesentery with enlarged lymphatic vessels. The abdominal cavity was carefully inspected for associated pathologies, but there was no specific pathology related to chylous ascites. After a peritoneal lavage with warm saline solution and the insertion of drains, the midline incision was closed.

The patient's recovery period was uneventful. He received nothing peroral for 5 days and then was gradually given a full (fat-free) diet. During five-day period, he received intravenous antibiotics (ceftriaxone 1 g ×2), total parenteral nutrition, and octreotide acetate (Sandostatin) injection 2×0.1 mg/sc. In the first postoperative day, the maximum amount of chylous drainage (250 cc) was observed (Figure 1), and less than 30 mL of serous fluid was detected on the second day. The laboratory investigation of the fluid from the drains showed the levels of triglyceride to be as high as 541 mg/dL. The results of the serum and drain fluid tests are shown in Table 1.

The drain was removed on the 5th day postoperatively, and he was discharged on the 7th day postoperatively. No bacterial growth or atypical cytology was observed in the evaluation of the acid fluid. The histopathological examination of the appendix showed acute edematous appendicitis. Thoraco-abdominal computed tomography and lymphoscintigraphy were performed in

Cite this paper as:
Kaya C, Yazıcı P, Kartal K, Bozkurt E, Mihmanlı M. A rare cause of acute abdomen: Chylous ascites. Turk J Surg 2017; 33(2): 123-125

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Received: 23.09.2014
Accepted: 02.12.2014
Available Online Date: 06.07.2015

Figure 1. The "chylous" fluid in the pelvic drainage catheter

Table 1. Comparative laboratory analysis of the fluid and the blood tests

Parameters	Drainage fluid	Simultaneous serum assays
Triglycerides	541 mg/dL	32 mg/dL
Cholesterol	92 mg/dL	60 mg/dL
Density	1020	-
Microprotein	3721.7 mg	-
Microalbumin	33.2 mg	-

the postoperative period for elucidating the acid etiology. No pathological findings were observed in these imaging tests.

DISCUSSION

Acute chylous peritonitis results from a sudden outpour of chyle into the peritoneal cavity (4). Chylous ascites can be caused by many reasons such as peritoneal bacterial infections, parasitic diseases, tuberculosis, liver cirrhosis, malignant tumors, surgery, blunt abdominal trauma, and congenital defects of the lymphatic system (1, 5). In adults, cancer is the most frequent cause of chylous ascites.

Chylous ascites also can spontaneously occur in some patients with no discernible etiologic factor. In medical literature, acute chylous peritonitis is most frequently diagnosed in young adults mostly during surgery for acute appendicitis (6). Likewise, in this case, the preoperative diagnostic tests were suspicious for acute appendicitis. In patients with chylous ascites, the loculation of ascitic fluid is generally observed in the right paracolic area; therefore, right lower quadrant pain is the most prominent symptom. In medical literature, we found five patients with spontaneous chylous ascites that clinically mimic acute appendicitis. As in our case, none of these patients had a significant reason for the etiology of ascites (7, 8).

Diagnostic methods, including computed tomography, lymphangiography, and lymphoscintigraphy, are of great importance for the investigation of the etiology of chylous ascites. With lymphoscintigraphy, lymph flow rate and peritoneal fistulas can be evaluated (8). In our study, however, lymphoscintigraphy was not useful to detect the leak, probably because of low output chyle leak.

The treatment options of chylous peritonitis are based on the underlying diseases. Surgery can be effective in both diagnosis and treatment. Laparoscopic exploration can be an alternative to open surgical techniques and may be beneficial for the postoperative period (9). Drainage catheter placement next to the probable source of the leakage observed is useful to examine the volume and efficacy of the treatment in the follow-up period. A low-fat diet rich in medium-chain triglycerides for reducing lymphatic flow is suggested to be effective in the treatment. This type of diet would be more effective, especially if the leakage is secondary to the intestinal lymphatic system. Parenteral nutrition and octreotide treatment can substantially reduce chylous ascites resulting in low lymphatic flow (7, 10, 11).

CONCLUSION

Chylous peritonitis is a very rare condition, which can cause acute abdomen. A meticulous exploration should be performed for elucidating the etiology. The choice of surgical technique depends on the experience of the surgical team. In the postoperative period, diagnostic tests may be helpful to clarify the etiopathogenesis.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.K., K.K.; Design - P.Y., K.K.; Supervision - P.Y., M.M.; Funding - E.B., C.K.; Materials - E.B., K.K.; Data Collection and/or Processing - E.B., C.K.; Analysis and/or Interpretation - C.K., M.M.; Literature Review - E.B., C.K.; Writer - P.Y., K.K., C.K.; Critical Review - P.Y., M.M.

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

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

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Turk J Surg 2017; 33: 126-129
DOI: 10.5152/UCD.2015.2933

Case Report

Portal vein thrombosis as a rare cause of abdominal pain: When to consider?

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ABSTRACT

Extrahepatic portal vein thrombosis (PVT) is a rare condition that is characterized by the presence of thrombus within any segment of the portal vein, including the right and left intrahepatic branches. It may also extend to the splenic or superior mesenteric veins. Portal vein thrombosis may be related to cirrhosis or liver malignancy as well as to local inflammatory conditions in the abdomen and genetic or acquired thrombophilic diseases. Currently, PVT is being increasingly diagnosed due to advances in modern imaging techniques. The clinical presentation has a wide range, from an asymptomatic lesion to a potentially life-threatening situation. In this study, we present three patients with PVT. The diagnosis was made by radiologic and clinical findings. In the first patient, genetic testing revealed factor V Leiden mutation as the cause of PVT. The second patient was diagnosed with lupus anticoagulant syndrome as the cause of PVT. Portal vein thrombosis was associated with intra abdominal infection due to anastomotic leakage in the third patient. Two patients were successfully treated with anticoagulant therapy. This report emphasizes that even though PVT is a rare cause of abdominal pain, timely diagnosis and appropriate management is vital due to its lethal complications such as mesenteric ischemia and mesenteric infarct.

Keywords: Anti coagulation treatment, factor V Leiden mutation, portal vein thrombosis

INTRODUCTION

Portal vein thrombosis (PVT) was first reported in a patient with liver cirrhosis, with detection of phlebothrombosis in the portal system, in 1869 (1). Portal vein thrombosis is a rare condition characterized by presence of luminal partial or complete thrombosis in any segment of the portal vein including the left intrahepatic branches. It may even spread to the splenic or superior mesenteric veins. Currently, portal vein thrombosis is detected more often owing to the improvements in modern imaging techniques. Its clinical spectrum varies from asymptomatic presentation to life-threatening conditions. Patients may present with various clinical manifestations ranging from vague abdominal pain to sepsis resulting from ischemic necrosis-associated perforation. It may be associated with cirrhosis or liver malignancy, as well as with local inflammatory conditions of the abdomen, and congenital or acquired prothrombotic diseases. Timely and proper interventions reduce mortality and morbidity rates associated with PVT (1, 2).

This study aimed to review the clinical characteristics and treatment of PVT based on three patients, each with different clinical presentations, along with a literature review.

CASE PRESENTATIONS

Case 1. A 53-year-old female patient. She complained of mild abdominal pain for the last three days. Her family history was insignificant. She has been diagnosed with Diabetes Mellitus about 1 month ago. There was no pathological finding on her physical examination except minimal sensitivity on the right upper quadrant of the abdomen. The computed tomography (CT) and abdominal color doppler ultrasonography revealed thrombus in the main portal vein and its intrahepatic branches. Further examination of the patient showed Factor 5 Leiden mutation (FVL). The patient was started on subcutaneous bid 0.6 mL of low molecular weight heparin (LMWH) with a diagnosis of PVT, which was shifted to oral anticoagulation. The general condition of the patient is good and she is currently being followed-up in the outpatient clinics.

Case 2. A 16-year-old male patient. An incidental appendectomy operation has been performed 10 days prior to admission in our hospital. The operation has been performed in another hospital where he presented with complaints of abdominal pain, nausea and vomiting, with a preliminary diagnosis of acute abdomen, and he underwent appendectomy since there was no pathologic finding except intra-abdominal free fluid. The patient was referred to our clinic for further evaluation since his complaints continued. On physical examination, there was non-specific sensitivity in the abdomen and no sign of acute abdomen.

Cite this paper as:
Tavusbay C, Kamer E, Acar T, Kokulu İ, Kar H, Gür Ö. Portal vein thrombosis as a rare cause of abdominal pain: When to consider? Turk J Surg 2017; 33(2): 126-129

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Received: 30.09.2014
Accepted: 15.12.2014
Available Online Date: 02.07.2015

The pathologic laboratory values included a white blood cell count of 13.100/ul (3.5-10), hematocrit level of 33%, and creatinine kinase of 1706 U/L (30-200). Computed tomography and doppler ultrasonography revealed PVT, large collateral veins at the level of the porta hepatis and diffuse peritoneal fluid in the abdominal cavity (Figure 1, 2). Lupus anticoagulant antibodies were found to be elevated in further evaluation. The patient was started on LMWH. He is currently on oral anticoagulation without any problems.

Case 3. A 64-year-old male patient. The patient has undergone an emergency operation 20 days ago in another clinic due to acute abdomen and received partial small bowel resection and end-to-end anastomosis due to small bowel necrosis associated with mesenteric ischemia. In the postoperative period, the patient was admitted to our emergency clinic due to biliary drainage from the abdominal drain. On physical examination, he had extensive brown rashes throughout his body as well as numerous fibromas. The computed tomography showed bilateral pleural effusion, an appearance compatible with thrombosis in the portal vein, diffuse peritoneal free fluid, and splenic infarcts. Anti-thrombolytic therapy was initiated. A laparotomy was performed after the patient's evaluations and resuscitation were completed. On laparotomy, intense adhesions related to the previous operation was detected within the abdomen along with severe edema on the intestinal walls and the peritoneum. Any site of leakage was not observed.

The general condition of the patient improved in the early postoperative period. He tolerated oral diet. On the 6th postoperative day, however, he developed convulsions and sudden respiratory arrest. The patient was immediately intubated and transferred to the intensive care unit. Cranial magnetic resonance imaging (MRI) and CT revealed an appearance consistent with intracranial plexiform neurofibromas (Neurofibromatosis type 1). As his medical treatment continued, the general condition of the patient deteriorated mainly due to his neurological status and he died at the 46th day of follow-up.

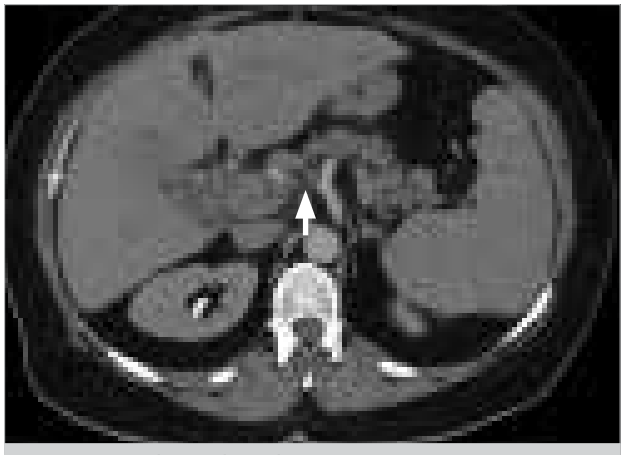

Figure 1. Portal vein thrombosis

All patients were informed in detail about the disease and the procedures to be performed, and a patient informed consent form was obtained from all. The required approvals were obtained from patients in order to carry out scientific studies.

DISCUSSION

The likelihood of developing PVT throughout life is around 1% in the general population (1). In patients with cirrhosis, this incidence is reported to be between 0.6-16% according to the severity of cirrhosis and the incidence is even higher in patients requiring liver transplantation. The incidence is 10-40% in patients with liver cancer (1). As seen in Table 1 various factors can cause PVT (1- 3). The rate of patients in whom no etiologic factor can be detected, who are accepted as idiopathic, is stated as 8-15% (1).

Clinical findings vary from patient to patient and are usually non-specific. Although there is a tradition to classify portal vein thrombosis as acute and chronic, it is not always clinically possible to differentiate between the two. Some authors define PVT as acute if the initial clinical manifestations had begun 60 days prior to diagnosis, but this opinion is not universally accepted (1). Acute and chronic PVT are defined as sequential stages of the same disease that occur for similar reasons, but their clinical treatments differ. Acute septic PVT, also called pylephlebitis, is characterized by the presence of infected thrombosis in the portal vein. Usually there is a septic focus in the abdomen. Acute PVT is often asymptomatic or manifests with mild pain, and is generally a coincidental finding on abdominal imaging performed for other causes. However, SMV and mesenteric arc involvement can present with hematochezia due to congestion and ischemia in the intestine depending on the severity of involvement, or can manifest as multiple organ failure ranging from shock, sepsis and even death. Chronic PVT can be asymptomatic and can be detected incidentally on imaging methods. Collateral development (portal cavernous) occurs around the thrombotic portal vein. In these patients, signs of portal hypertension such as splenomegaly, esophageal varices, anemia, and thrombocytopenia can be detected. Upper GI bleeding can be the first symptom in

Table 1. Etiology of portal vein thrombosis (PVT)

Local factors	Pro-thrombotic factors
1. Cirrhosis	1. Genetic factors:
2. Abdominal organ malignant diseases; liver and pancreas primarily	a) Mutation; Factor V Leiden, Factor II
3. Infection and inflammation; pancreatitis, diverticulitis, cholecystitis, appendicitis, neonatal omphalitis etc.	b) Deficiencies: Protein C, Protein S deficiency, Antithrombin deficiency
4. Portal vein injury; abdominal surgery, blunt trauma, surgical shunts and transjugular intrahepatic porto-systemic shunt, splenectomy and liver transplantation, etc	2. Acquired factors:
	Myeloproliferative diseases, antiphospolipid syndrome, paroxysmal nocturnal hemoglobinuria, pregnancy, oral contraceptive pills, hyperhomocysteinemia, malignancy
	3. Idiopathic 10-30%

20-40% of cases. The prognosis in chronic cases is largely dependent on the presence of underlying cirrhosis or malignancy. The prognosis of portal vein thrombosis in patients without cirrhosis or malignant disease is better than the others. The clinical significance of incidentally detected PVT is unclear.

Imaging methods used for the diagnosis of portal vein thrombosis include Doppler US, abdominal CT and MR. The specificity and sensitivity of Doppler US is reported to be 80-100% (3,4). Endoscopic ultrasonography was reported to be 81% sensitive and 93% specific for the diagnosis of portal vein thrombosis, and may aid in identifying small thrombi which do not produce complete thrombosis (4). Patients with portal vein thrombosis may have normal liver function tests as well as other laboratory tests, except cirrhotic patients. A slight decrease in prothrombin and other coagulation factors, and an increase in D-dimer levels may be detected. Laboratory findings are mostly nonspecific as clinical findings, nevertheless, laboratory findings of any disease and/or genetic disorder associated with PVT can be determined.

In our first case, a factor V Leiden (FVL) heterozygote mutation was detected. FVL mutation, one of the rare causes of portal venous thrombosis, is a hereditary clotting disorder resulting from the substitution of arginine with glutamine at position 506 in the Factor V gene. It is detected in 3-12% of healthy individuals worldwide, and in 9% of healthy individuals in our country. Portal vein thrombosis is common among these patients (5). Some authors suggest systemic screening for the presence of thrombotic factors in patients with a history of portal venous thrombosis, even if local causes are present (3, 6).

In our second patient, antiphospholipid syndrome was detected. Antiphospholipid syndrome (antiphospholipid antibody syndrome, APS) or Hughes syndrome is an autoimmune disorder characterized by coagulation disorders caused by antibodies to plasma proteins bound to phospholipids or anionic phospholipids. Antiphospholipid antibodies are a heterogeneous group of antibodies against negatively charged phospholipids, mainly anticardiolipin antibody and lupus anticoagulant antibody as well as phosphatidyl serine, phosphatidyl inositol and phosphatidic acid, and against neutral phosphatidyl etonalamine. Although hypercoagulability resulting from the presence of antiphospholipid antibodies could manifest only as a disorder in coagulation tests, it may also present with cerebrovascular events, venous thrombosis, arterial thrombosis, or obstetric complications. APS is a risk factor for portal venous thrombosis in non-cirrhotic patients (7).

Type 1 neurofibromatosis (NF-Type 1, Von Recklinghausen's disease) was detected in the third patient. The disease is autosomal dominant. Involvement of the skin, bone, soft tissue, arterial system and nervous system is accompanied by multiple sclerosis and malignancy development in various organs and tissues of the body. Association with APS that causes thrombotic disorders has also been reported (8).

In this study, different preliminary diagnoses were made clinically in 3 patients, and the diagnosis of PVT could be made by imaging methods. This indicates that the diagnosis can be easily missed in daily clinical practice. For this reason, PVT should be kept in mind especially in patients with vague abdominal pain. It has been reported that in cases with portal vein thrombosis, the primary etiology can be identified in a significant portion of the patients (70%) by advanced etiopathogenetic tests (7). The aim of treatment in acute PVT is to prevent further progression of thrombosis in the portal venous system and to treat complications associated with PVT (Table 2). There are few randomized studies on this issue. For this reason, the treatment should be individualized. Portal vein thrombosis may spontaneously resolve. However, it is crucial to implement treatment methods for portal vein thrombosis before serious complications arise. Treatment options in these patients include anticoagulant therapy, surgical thrombectomy, endovascular thrombectomy, and thrombolytic therapy. It has been reported that portal vein thrombus was recanalized with anticoagulant therapy in more than 80% of patients (3). Thrombolytic therapy can also be used, but there are reservations about the use of systemic thrombolytics.

CONCLUSION

In conclusion, PVT should be considered as part of differential diagnosis in non-specific abdominal pain. In particular, it should be considered in the differential diagnosis of unexplained abdominal pain in patients with intra-abdominal infection and those with previous abdominal surgery including laparoscopic procedures, and both radiologic and laboratory methods should be used for diagnosis. We emphasize the need for timely diagnosis and appropriate treatment of PVT, since although it is a rare cause of abdominal pain it may present with lethal complications such as mesenteric ischemia and infarction.

Table 2. PVT treatment (Based on AASLD)

Acute PVT	Chronic PVT
All patients should receive anticoagulation therapy for at least 3 months.	All patients should be screened for esophageal varices.
Treatment is started with low molecular weight heparin (LMWH).	Treatment should be applied for active variceal hemorrhage and for primary and secondary prophylaxis according to guidelines for cirrhotic patients.
Treatment is shifted to oral anticoagulation once the patient has stabilized and if no invasive procedure is planned.	Long term anticoagulation is considered • in patients without cirrhosis and with permanent thrombotic risk factors that are not otherwise correctable if there is no contraindication.
Long term anticoagulation is considered • in patients with permanent thrombotic risk factors that are not otherwise correctable, • in patients without a contraindication and thrombus extension into mesenteric veins.	In patients with gastroesophageal varices, adequate prophylaxis for variceal bleeding should be started before anticoagulation treatment.
Antibiotics are initiated if there is any evidence of infection.	

PVT: portal vein thrombosis

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.T., E.K., T.A., İ.K., H.K., Ö.G.; Design - E.K., T.A., İ.K., H.K., Ö.G.; Supervision - E.K., T.A., İ.K., H.K., Ö.G.; Funding - C.T., T.A.; Materials - Ö.G., İ.K.; Data Collection and/or Processing - C.T., T.A.; Analysis and/or Interpretation - E.K., T.A.; Literature Review - C.T.; Writer - C.T., E.K.; Critical Review - T.A., İ.K., Ö.G.

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

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

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Turk J Surg 2017; 33: 130-132
DOI: 10.5152/UCD.2015.2966

Case Report

Incidental gastrointestinal stromal tumor at a gastroscopic polypectomy specimen: A case report and review of literature

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ABSTRACT

Although gastrointestinal stromal tumors (GISTs) comprise less than 1% of all gastrointestinal (GI) tract tumors, they are the most common mesenchymal tumors of the GI tract. Gastrointestinal stromal tumors can occur anywhere along the GI tract, but the stomach and small intestine are the most frequently involved sites. Gastrointestinal stromal tumors are frequently asymptomatic, and one-third of all cases are found incidentally. Endoscopy, endoscopic ultrasonography, and computed tomography are useful tools in the diagnosis. Endoscopic mucosal resection, endoscopic submucosal dissection, laparoscopic endoscopic cooperative surgery, and surgery with either laparoscopic or open approaches are treatment modalities for GISTs. An R0 resection is the principle surgery. Imatinib is the main medical agent used in the adjuvant or neoadjuvant treatment of GIST. We present a 65-year-old woman with an asymptomatic GIST that arose from a gastric polyp treated via endoscopic polypectomy.

Keywords: Gastric submucosal tumor, gastrointestinal stromal tumor, endoscopic treatment

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract (80%) and comprise less than 1% of all gastrointestinal tumors and 5% of all sarcomas (1). Gastrointestinal stromal tumors arise from the interstitial cells of Cajal that are located in the submucosal and myenteric plexus of the gastrointestinal tract. Gastrointestinal stromal tumors are primarily seen in the middle-aged and elderly population, and there is no gender difference. Gastrointestinal stromal tumors frequently occur in the stomach (60%), small intestine (30%). Less frequently, GISTs may arise from the duodenum, colon, rectum, and mesentery. Although most of the patients are asymptomatic and one-third of all cases are found incidentally (2), gastrointestinal bleeding, abdominal pain, and discomfort are the main symptoms of GISTs (3). Endoscopy, endoscopic ultrasonography, computerized tomography, and magnetic resonance imaging are useful diagnostic modalities for GISTs (2, 3). Pathological diagnosis is based on immunohistochemical staining with c-KIT, alpha-type platelet-derived growth factor receptor, and protein kinase C theta (2). Surgery with either laparoscopic or open approaches is the mainstay of treatment for non-metastatic GISTs; however, the routine removal of lymph nodes is not necessary (2, 4). Endoscopic enucleation and endoscopic submucosal resection can be used in selected patients. The c-kit tyrosine kinase inhibitor imatinib was found to be useful in treating GISTs. We present a 65-year-old woman with an asymptomatic GIST that arose from a gastric polyp, which was incidentally treated by endoscopic polypectomy.

CASE PRESENTATION

A 65-year old woman with 6-month history of dyspepsia was admitted to us. Epigastric tenderness was the only symptom found at the physical examination. All biochemical studies were normal. Upper gastrointestinal endoscopy detected a 1 cm × 1 cm well-circumscribed submucosal polypoid lesion at the gastric fundus (Figure 1a). The lesion was mobile, and it felt hard during biopsy. Snare polypectomy was performed after submucosal elevation by the injection of normal saline (Figure 1b). The histological examination revealed GIST at the biopsy specimen, and the tumor diameter was 4.5 mm. The tumor was confined to the submucosa, and the surgical margins were negative. There was no mitosis, and the Ki-67 index was under 1% (Figure 2a). The tumor was immunohistochemically positive for CD117 (also known as c-kit) (Figure 2b) and CD34 (Figure 2c), and it was immunohistochemically negative for muscle-specific actin, smooth muscle actin, desmin, kromogranin, synaptophysin, and neuron-specific enolase. Therefore, histologically submucosal, a low-risk GIST (Figure 2d) was reported in the pathology report. There was no local or distant metastasis on the computed tomography scan. Adjuvant treatment was not planned because of the risk stratification of the tumor by mitotic index and tumor size and location. Her control evaluations in the postoperative follow-up at the sixth month were normal. Informed consent was obtained from the patient.

Cite this paper as:
Karakaş DÖ, Dandin Ö, Balta AZ, Özdemir Y, Yılmaz İ, Sücüllü İ. Incidental gastrointestinal stromal tumor at a gastroscopic polypectomy specimen: A case report and review of literature. Turk J Surg 2017; 33(2): 130-132

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Received: 07.11.2014
Accepted: 12.12.2014
Available Online Date: 06.07.2015

DISCUSSION

The principle surgery for GISTs is R0 resection of the tumor. Rather than systemic lymphadenectomy, adjacent enlarged lymphadenectomy is required. The recommended size of the tumor for laparoscopic resection in GIST treatment is ≤2 cm. Also, laparoscopic wedge resection is superior to the open approach (4).

Recommended laparoscopic approaches for gastric GIST are gastric wedge and transgastric tumor-everting resection for the posterior wall-located tumors that grow toward the cavity and proximal or distal gastrectomy for larger stromal tumors located in the cardia, pylorus, and gastric antrum. Recommended open approaches are subtotal gastrectomy for larger tumors located near the cardia or pylorus and gastric resection for larger tumors at the side of the lesser curvature. Compared with open resection, the laparoscopic resection of gastric stromal tumors is associated with a shorter operation time and hospital stay and a lower recurrence rate (5). The laparoscopic and open surgical approaches have a risk of hemorrhage and intra-peritoneal dissemination because GISTs tend to have a friable consistency (6).

Huang et al. (7) reported that endoscopic therapies for gastric GISTs are endoscopic ligation and resection (ELR), endoscopic submucosal excavation (ESE), and endoscopic full-thickness resection (EFR). ELR was performed for tumors smaller than 1.2 cm and when perforation was seen. ESE was performed for tumors larger than 1.5 cm and when no perforation occurred. EFR was performed for tumors larger than 2 cm and when artificial perforation occurred as a complication.

Endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or modified ESD are other endoscopic treatment choices for gastric GISTs. EMR can be performed for tumors smaller than 2 cm with lower en bloc resection and a higher local recurrence rate. ESD or modified ESD can be performed for tumors larger than 2 cm with a higher en bloc resection and lower local recurrence, perforation, and bleeding rates (8). Zhang et al. (9) reported that ESD is a safe, effective, well-tolerated, and minimally invasive therapy with few complications such as perforation of the intraluminal gastric submucosal tumors originating from the muscularis propria, which can be managed endoscopically.

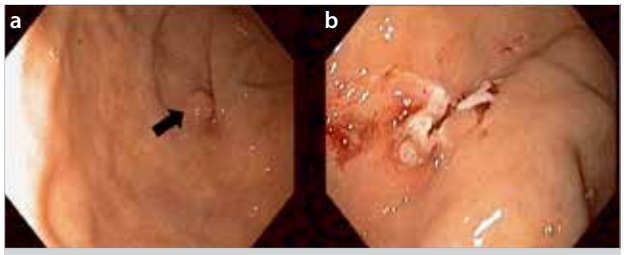

Figure 1. a, b. (a) Endoscopic image of polypoid lesion at the fundus. (b) Postpolypectomy image of the fundus

Laparoscopic and endoscopic cooperative surgery (LECS) is another endoscopic treatment choice for gastric GISTs. LECS can be divided into the following two types: laparoscopic-assisted endoscopic technique and endoscopic-assisted laparoscopic technique. LECS is safe, easy, and beneficial for the laparoscopic resection of gastric GIST. LECS has a shorter operative time and a low bleeding risk with reduced intra-abdominal contamination and infection than ESD (10).

CONCLUSION

Gastrointestinal stromal tumors should be treated as possible with laparoscopic or endoscopic methods according to the development of technology and the increasing interest of surgeons to minimally invasive approach currently. Endoscopic treatment is a safe, easy, well-tolerated, and minimal invasive treatment choice for incidental gastric submucosal tumors smaller than 2 cm with a lower complication rate.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.Ö.K., A.Z.B.; Design - A.Z.B.; Supervision - Y.Ö.; Data Collection and/or Processing - A.Z.B., İ.Y.; Analysis and/or Interpretation - A.Z.B., Ö.D.; Literature Review - D.Ö.K.; Writer - D.Ö.K.; Critical Review - Y.Ö., İ.S.

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

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

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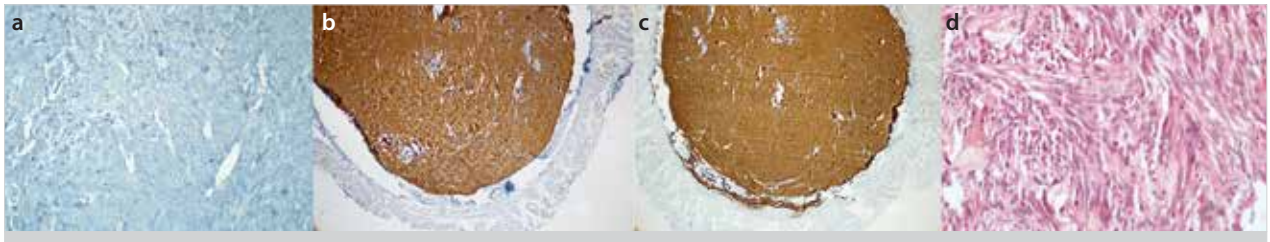

Figure 2. a-d. (a) ×100 microscopic magnification of the Ki 67 index. (b) ×40 microscopic magnification of the CD117-stained tumor. (c) ×40 microscopic magnification of the CD34-stained tumor. (d) ×400 microscopic magnification of the hematoxylin–eosin-stained stromal tumor

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Turk J Surg 2017; 33: 133-134
DOI: 10.5152/UCD.2015.2927

Case Report

Epidermal cyst mimicking incision line metastasis

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ABSTRACT

Epidermal cysts are cystic tumors lined with keratinized squamous layer and filled with keratin debris. Epidermal cysts may develop by implantation of surface epidermal layer into the dermis or subcutaneous tissue after trauma or surgical procedures. Cervix cancer spreads either directly or via the vascular and lymphatic systems. Distant skin metastasis of endometrium or cervix cancer is very rare. In this case report, a patient who had a history of cervix cancer operation 11 years ago and presented with a mass that mimicked incision line metastasis and was histopathologically diagnosed with epidermal cyst is presented.

Keywords: Epidermal cyst, cervix cancer, incision line metastasis

INTRODUCTION

Epidermal cysts are cystic tumors containing keratin surrounded by keratinized squamous epithelium (1). Epidermal cysts are mostly located in the palms and fingers, while they can be detected in any part of the body (2). Acquired epidermal cysts are related with implantation of superficial epidermal tissue into the dermis or subcutaneous tissue after trauma or surgical intervention (2). Cervical cancer spreads via direct invasion, hematogenous and lymphatic dissemination (3). Skin metastasis of endometrium and cervical cancer is very rare (4).

Herein we report a patient, with a history of cervical cancer surgery 11 years ago, who was diagnosed with a calcified proliferative epidermal cyst that mimicked incision line metastasis.

CASE PRESENTATION

A 63-year-old female patient has been admitted to a health institution due to abnormal uterine bleeding in 2003. Her cervical biopsy has revealed squamous cell carcinoma. The patient has undergone total abdominal hysterectomy, bilateral salphingoooferectomy and pelvic paraaortic lymph node dissection. Histopathologic examination has been reported as squamous cell carcinoma and she has received 6 cycles of chemotherapy and radiotherapy. No additional problems have been identified in routine oncologic controls since 2003. The patient, who had stiffness and scarring in the incision line for about 2 months, presented to our hospital dermatology outpatient clinics. On dermatologic examination, a 2.5x2 cm in diameter, irregular bordered, circumferentially hyperemic, infected, ulcerated, painless semimobile mass was observed in the left paramedian incision scar. The patient was consulted to general surgery and an infected tumor metastasis could not be ruled out. An oral-intravenous contrast enhanced computed tomography was obtained, which revealed scar tissue in the lower left part of the abdomen secondary to the surgical procedure along with nodular skin thickening and contrast enhanced calcified areas at this level, and tumor metastasis could not be ruled out (Figure 1).

No abnormality was detected in her laboratory parameters. An operation was planned because the patient's findings could not be differentiated from tumor metastasis. Total excision was performed by obtaining a macroscopic intact surgical margin to include the old operation scar and the infected mass. The patient was discharged without any problems on the first day after the operation. Histopathological examination revealed ruptured mixed inflammatory proliferative epidermal cyst.

A detailed informed patient consent form was obtained for the presentation of this case.

DISCUSSION

Epidermal cysts are most common in the young and middle ages, with equal frequency among men and women. Clinically they appear as painless, slow-growing, regular bordered lesions. Symptoms may occur in 6 months or in 20 years. The malignant conversion is rare. Macroscopically, they are usually greater than 3 cm in size (5). Cervical cancer is the second most common cancer type among women in

Cite this paper as:
Gündoğdu R, Ayhan E, Çolak T. Epidermal cyst mimicking incision line metastasis. Turk J Surg 2017; 33(2): 133-134

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Received: 14.10.2014
Accepted: 26.12.2014
Available Online Date: 02.07.2015

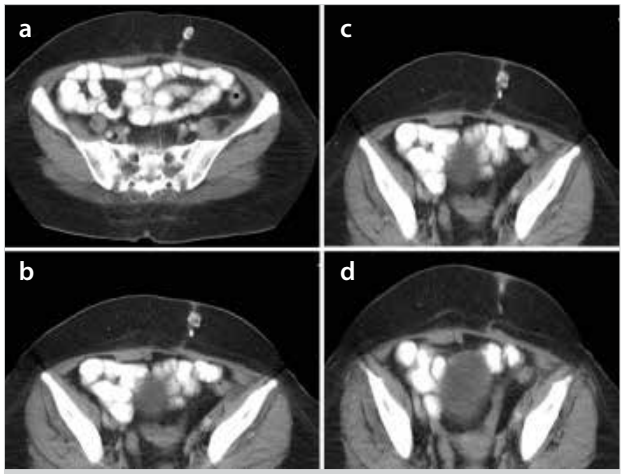

Figure 1. a-d. Mass lesion with nodular calcified zones in the incision line

the world. In Turkey, it is the 9th most common cancer among women and is ranked 13th among causes of cancer-related death (6). Cervical cancer spreads via direct invasion, hematogenous and lymphatic dissemination (3). Skin metastasis of endometrium and cervical cancer is very rare. The incidence ranges between 0.1 and 2% (4). There are reports in the literature that the interval between cervical cancer surgery and diagnosis of skin metastasis may be 1-70 months (7). The most common type of cancers with skin incision metastasis have been reported as colon, kidney and bladder cancer (8).

Our patient had a history of surgical operation 11 years ago. The location of the lesion on the incision line, the oncologic history of the patient, the ulceration and induration on the mass and the skin led to a suspicion of tumor metastasis.

Acquired epidermal cysts develop with implantation of superficial epidermal tissue into the dermis or subcutaneous tissue after trauma or surgical intervention (2). The lesions become visible after a traumatic event in a period of months to years (9). These lesions most commonly occur in the distal fingers of males and females aged 30 to 40 years (10). In the literature, epidermoid cyst that developed after 5 years in a patient who has undergone mastoidectomy due to cholestatoma (1), and epidermal cyst cases in the incision line following ear surgery has been reported (2).

CONCLUSION

The rare incision line epidermal cyst may mimic tumor metastasis in patients with a history of tumor surgery. It should be kept in mind that chronic wounds and masses formed in the incision line may rarely be tumor metastasis while they may be related to benign causes such as epidermal cysts. Histopathologic examination should be performed for their differential diagnosis.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.G., E.A.; Design - R.G.; Supervision - R.G.; Funding - R.G.; Data Collection and/or Processing - R.G.; Analysis and/or Interpretation - R.G., E.A.; Literature Review - R.G., E.A.; Writer - R.G., T.Ç.; Critical Review - T.Ç.

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

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

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