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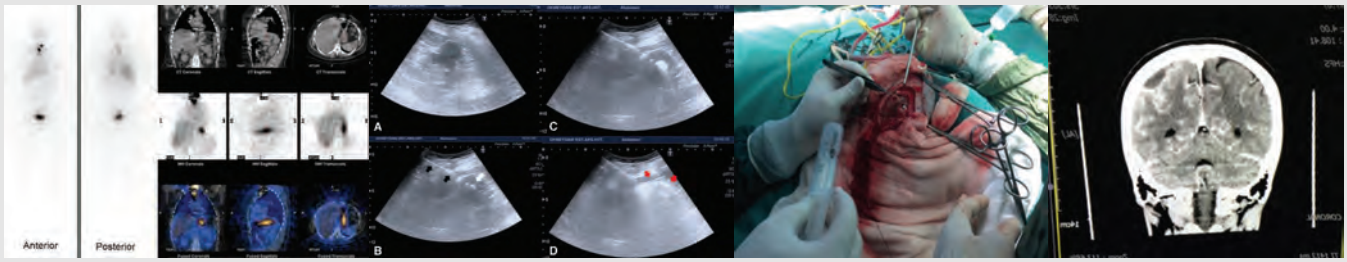

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All manuscripts should be submitted in 12 point Times New Roman type with 2 line spacing.

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- Name(s), affiliations, highest academic degree(s), e-mail addresses, and ORCID IDs of the author(s),
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- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
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Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, 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, Methods, Results, Discussion, and 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

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separate subheading under the Materials 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).

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

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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.

Case Series: The Case Series section reports a series of 2-6 similar cases. The cases should address a challenging diagnostic and/or therapeutic problem with possible solutions to help clinicians in managing these cases. Case series must be accompanied with a comprehensive review of literature. It should include six authors maximum. Structure of manuscript should include Introduction, Case Series, Discussion, Conclusion. It should have 3-5 keywords maximum. Please check Table 1 for the entire limitations for Case Series.

Interesting Image: No manuscript text is required. Interesting Image submissions must include the following:

Title Page (see Original article section)

Abstract: Approximately 100-150 words; without structural divisions; in English and in Turkish. Turkish abstract will be provided by the editorial office for the authors who are not Turkish speakers. If you are not a native Turkish speaker, please re-enter your English abstract to the area provided for the Turkish abstract.

Image(s): The number of images is left to the discretion of the author. (See Original article section)

Figure Legend: Reference citations should appear in the legends, not in the abstract. Since there is no manuscript text, the legends for illustrations should be prepared in considerable detail but should be no more than 500 words total. The case should be presented and discussed in the Figure legend section.

References: Maximum eight references (see Original article section).

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).

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review Article	5000	250	80	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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

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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: Stephane A. Management of Congenital Cholesteatoma with Otoendoscopic Surgery: Case Report. Turkiye Klinikleri J Med Sci 2010;30:803-7.

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 Dçent 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/ncidodlEID/cid.htm.

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Measles-Mumps-Rubella Vaccination of Patients with Egg Allergy: One Center Experience

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Abstract

Objective: Measles-Mumps-Rubella (MMR) vaccine is a live vaccine. Measles and mumps are cultured in chick embryo fibroblasts, and rubella is cultured in human diploid cell culture. MMR vaccine contains egg protein and there are concerns among health care providers while practicing this vaccine in children with history of egg allergy in primary health centers. In this study we share the clinical characteristics and MMR vaccination experiences of cases with egg allergy, who applied to well-child care and allergy-immunology outpatient clinics.

Methods: Cases who had egg allergy and who were referred to well-child care and allergy-immunology outpatient clinics for vaccination between January 2017 and September 2018 were included in the study. The cases were firstly evaluated by a pediatric allergy-immunology specialist and egg allergy was confirmed as a diagnosis. Families were informed about possible side effects. The cases were kept under clinical supervision for at least 1 hour after vaccination.

Results: Sixty-one cases with egg allergy were included in the study. Twenty-eight (45.9%) of them were female. None of the cases had allergic reactions after MMR vaccination. The average time of vaccination of 52 cases who reached the allergy-immunology outpatient clinic before 1 year of age and were examined here was 379 days. Nine cases were directed by the primary health center for vaccination at the age of 1 year. The average time of vaccination of these 9 cases was 400 days.

Conclusion: It is seen that MMR vaccination can safely be applied to the cases with egg allergy by taking routine precautions. It is important to train the physicians working in primary health centers about allergic reactions that may develop after vaccinations in order to prevent anaphylaxis cases and to prevent delays in vaccinations.

Keywords: Vaccination, egg allergy, Measles-Mumps-Rubella vaccine

INTRODUCTION

Routine vaccination is a very important public health practice that reduces the mortality and morbidity of many infectious diseases (1). Vaccines contain active antigens, conjugating antigens, preservatives, stabilizers, antimicrobial agents, adjuvants, and culture media (2). Gelatin which is used as a stabilizer in vaccines, neomycin, polymyxin B and streptomycin added to prevent vaccine contamination are the most known allergic vaccine components. The Measles-Mumps-Rubella (MMR) vaccines are live vaccines containing virus strains. Vaccinated mumps and measles strains are produced in chicken embryo tissue culture, while rubella strain is produced in human diploid cells. Therefore, there is egg protein in the MMR vaccine, but it is at a picogram level and is too low to cause an allergic reaction (3-5).

The most common acute allergic reactions after vaccination are IgE-mediated type 1 hypersensitivity reactions, with an average incidence of 0.22/100,000 doses (6,7). It has been determined that 31% of the vaccination caused allergic reactions occur with the first vaccination. In patients with moderate to severe egg

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allergy, no relationship was found between allergic reaction after MMR vaccine and skin prick test. First of all, hypersensitivity reactions that occur after the MMR vaccine are thought to occur due to non-egg proteins in the vaccine (2,8,9).

Studies have shown that if there is accompanying asthma in cases with egg allergy, it poses a risk for anaphylaxis that may develop after vaccination (4,10,11). In addition, it is stated that performing skin prick test before vaccination increases the risk of allergic reactions that may develop (12).

METHODS

Cases with egg allergy were followed up in the pediatric allergy-immunology outpatient clinic and referred to the normal pediatric outpatient and pediatric allergy-immunology outpatient clinic to be vaccinated between January 2017 and September 2018 are cases were evaluated retrospectively. The cases were primarily assessed by a child allergy-immunologist. In the cases, the diagnosis of egg allergy was made with a history of reaction associated with egg consumption, a blistering of 3 mm with egg yolk and/or egg white in the skin prick test or egg specific IgE above 0.35 kU/L. In cases with a suspected history, a nutrient loading test was performed with eggs and patients with positive reactions were considered to have egg allergies.

The patients' families were informed about possible side effects. Vaccinations of 2 cases with a history of anaphylaxis with food intake and 5 cases with a history of angioedema were vaccinated under observation for 2 hours. Other cases were kept under observation for at least 1 hour after vaccination and families were informed after vaccination and released.

For this study, ethics committee approval was obtained from the Clinical Research Ethics Committee of Okmeydanı Training and Research Hospital (approval date: 19.02.2019 no: 1142). Since our study was a retrospective study, patient consent was not obtained.

Statistical Analysis

SPSS 22.0 package program was used in the statistical analysis of the data, the results were expressed using the mean ± standard deviation, median (minimum value-maximum value) and number (%) depending on whether the data were parametric. Kolmogorov-Smirnov test was used to evaluate the suitability of quantitative data for normal distribution.

RESULTS

Sixty one cases with egg allergy were included in the study. Twenty eight (45.9%) of the cases were female and 33 (54.09%) were male and the onset of allergic symptoms that developed was 1 month at the earliest, and atopic dermatitis was developed as urticaria at the latest 11.5 months (Table 1). In 25 of the 61 cases, there was cow's milk and/or multiple food allergies along with egg allergies (Table 2). Egg specific IgE and immunoglobulin E levels of the patients are shown in Table 2.

The average of the days of vaccination of 52 cases who reached the child allergy policlinic before 1 year of age and were examined here was 379 days. Nine cases were directed to our hospital to be vaccinated by the family health center when the vaccination age of 1 year came. The average time of vaccination for these 9 cases was 400 days.

None of the 61 cases with detected egg allergy and vaccinated had any reaction with MMR vaccine. In one case, urticarial rash developed at the application area 15 minutes after varicella vaccination, it was observed that the rash resolved

Table 1. Demographic data of the cases and clinical findings in admission to the hospital

	Average ± standard deviation (median)	**The smallest - the largest**
Age when allergy first appeared (months)	5.16 months + 2.1 months	1-11.5 months
Age when applied to the hospital (months)	8.23 months + 2.1 months	3-13 months
Vaccination age (days)	383 + 21.46 (375)	365-454
Clinical picture in hospital admission	**n**	**%**
Anaphylaxis	2	3.2
Urticaria and angioedema	25	40.9
Atopic dermatitis	30	49.1
Proctocolitis only	4	6.5

Tablo 2. Other accompanying food allergies, laboratory findings

	n	**%**
Another accompanying food allergy	25	40.9
Cow's milk allergy	21	34.4
Multi food allergy	4	6.5
Laboratory values		
Egg yolk sp IgE >0.35	44	72.1
Egg white sp IgE >0.35	58	95.08
Number of patients had egg loading test	20	32.7
	Median	**The smallest - the largest**
Serum total IgE (kU/L)	40	0-564
Egg yolk specific IgE (kU/L)	0.40	0.01-38.0
Egg white specific IgE (kU/L)	1.23	0.05-74.9

IgE: Immunglobulin E

spontaneously within 1 hour, and was kept under observation for 4 hours.

DISCUSSION

In 1st Level Health Institutions, hesitation is experienced in vaccination of cases with egg allergy with MMR vaccine, cases are referred to 3rd Level Health Institutions and vaccination times are delayed. There are also reports from our country regarding allergic reactions developing after vaccination of children with milk and egg allergies in the form of a case report (13,14). In our study, while there is no delay observed on the vaccination time of the patients who applied to our clinic due to egg allergy before their vaccination time, it is seen that the age of 1 year vaccines are delayed in 9 cases where egg allergy is questioned when it is time for the 1 year vaccination.

Khakoo and Lack (4) stated that the amount of egg protein in MMR vaccines is very low, they do not expect allergic reactions that will develop with the vaccines, even the skin puncture test, but those who have serious symptoms should be vaccinated under hospital conditions. In the study of Aickin et al. (15) they did not see a reaction with the vaccine in cases with positive skin puncture test, so they stated that the skin prick test cannot predict the allergy that will develop with the vaccine. Nakayama et al. (16) reported the reaction after 366 MMR vaccines, in 34 of these cases developed anaphylaxis. From 27 of these anaphylaxis cases, serum specific IgE could be examined and sp IgE was positive against gelatin in 25/27 (93%) cases and it was shown that anaphylaxis occurred as a result of gelatin allergy. Upon this publication, gelatin has been removed from vaccines in Japan since 1998 and allergic reactions have almost disappeared after the MMR vaccine (17,18). The British Society of Allergy and Clinical Immunology guideline recommends that all children with egg allergy be vaccinated in primary health care facilities, but the children with anaphylaxis are evaluated by the allergist (19,20).

When we look at the 2018 circular of the Republic of Turkey Ministry of Health's Extended Immunization Program, it says "Anaphylactic reaction developing against a vaccine component creates definitive contraindications for all vaccines containing this substance". For MMR/Measles vaccines; the same circular states that the presence of an anaphylactic or anaphylactoid reaction against eggs (egg allergies other than anaphylaxis are not prevented) is a definite contraindication for these vaccines (21).

When we look at the MMR-II® vaccine package insert of the vaccines in our country; it states that if there is an anaphylactic or anaphylactoid reaction against eggs (egg allergies other than anaphylaxis are not prevented), there are certain contraindications (22).

In Priorix® vaccine package insert, it states that individuals with a history of anaphylactic, anaphylactoid or other rapidly developing reactions after eating eggs may be at increased risk for sudden hypersensitivity reactions after vaccination, although these types of reactions are very rare. People who have experienced anaphylaxis after eating eggs should be vaccinated very carefully with the necessary anaphylaxis treatment ready for this type of reaction (23).

In 61 cases with egg allergy in our clinic, no allergic reaction was observed after vaccination of the MMR, and in accordance with other studies, it was observed that the MMR vaccine can be safely administered in cases with egg allergy. However, it can be seen that anaphylaxis cases that may develop after both MMR and other vaccines cannot be prevented only by questioning egg allergy. Therefore, it is necessary to observe the cases for at least 60 minutes after each vaccination and ensure that the healthcare professionals working in the primary health care institution are competent to recognize and interfere with anaphylaxis (6).

Limitations of our study; since the data is retrospectively collected, there is a child immunology-allergy clinic in our center, and the patients who are followed are directed when it is time for the vaccination, we think that the vaccination times do not reflect the vaccine delays that may occur in our society.

CONCLUSION

In our study, no allergic reaction was observed after the MMR vaccine in cases with egg allergy. As suggested in many guides, we think that these cases can be vaccinated in primary health care facilities. However, in order to avoid delays in vaccination of allergic patients and to recognize the anaphylaxis cases that may develop after all vaccinations, we think that in-service training should be provided to healthcare professionals working in primary care institutions.

Ethics

Ethics Committee Approval: Clinical Research Ethics Committee of Okmeydanı Training and Research Hospital (approval date: 19.02.2019 no: 1142).

Informed Consent: This study was a retrospective study, patient consent was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Y., D.Ö., Concept: P.Y., Design: E.Y., D.Ö., Data Collection or Processing: P.Y., D.Ö., E.Y., Literature Search: D.Ö., E.Y., Writing: P.Y.

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ORIGINAL ARTICLE

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Retrospective Evaluation of Patients Diagnosed with Stage I-II Supradiaphragmatic Presentation Hodgkin's Lymphoma: Treatment Effect and Late-side Effect

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Abstract

Objective: The long-term treatment outcomes of patients with Hodgkin's lymphoma are important, as such patients have increased lifespans. Treatment options must be evaluated particularly for secondary malignancy risk and heart health.

Methods: We retrospective re-evaluated a total of 113 patients (all) who had received radiotherapy and/or chemotherapy for stage I-II disease out of 320 patients with Hodgkin's lymphoma who presented to and were treated at the Okmeydanı Training and Research Hospital Radiation Oncology Clinic between January 1974 and December 1997, and who then continued regular follow-up. I this period,only anterior mantle and anterior-posterior mantle treatment and/or chemoterapy, were evaluated for long-term side effects and efficacy.

Results: We compared 42 patients who had received only anterior radiotherapy (group 1) and 71 patients who had received anteroposterior radiotherapy (group 2). Recurrence was detected in 15 patients in group 1 and in 20 patients in group 2. Six patients in group 1 and 16 patients in group 2 died. The 5-year survival rate for group 1 and group 2 was 77.18% and 71.33%, respectively, and the respective 10-year survival rates were 70.8% and 67.16%. The secondary malignancies detected were lung cancer (3 patients), hemangiosarcoma (1 patient), larynx carcinoma (1 patient), neurofibromatosis (1 patient), and thyroid carcinoma (1 patient).

Conclusion: We discuss the patients' quality of life in addition to the possible late adverse effects of the treatments given the increased curability and survival in Hodgkin's lymphoma. The aim is to minimize the treatment-related adverse effects, given patients' longer life expectancy. For this reason, it is currently being tried to improve the quality of life and survival by reducing the risk of organs and heart doses in terms of secondary cancer such as lung and breast, ischemic heart disease by different methods such as anteror field radiotherapy. But still, giving up smoking and increasing physical activities must be recommended, particularly against lung cancer and ischemic heart disease.

Keywords: Hodgkin's lymphoma, anterior field radiotherapy, chemotherapy, secondary malignancy, ischemic heart disease

INTRODUCTION

Hodgkin's lymphoma has successfully been treated in our clinic with radiotherapy devices since the 1970s. The use of chemotherapy and radiotherapy has yielded better survival results. However, patients with long-term life expectancy develop various adverse effects, particularly cardiovascular disease, and treatment-associated secondary malignancies.

The Dutch researchers Schaapveld et al. (1) reported the secondary cancer risks of patients they had treated between 1965 and 2000. Van Nimwegen et al. (2) reported the association between radiotherapy and coronary arterial diseases in 1965-1995. Milgrom et al. (3) compared anterior field radiation and anteroposterior radiation for decreasing cardiac and secondary malignancy risk. Heart doses measured better in only anterior field radiation, and breast and lung doses measured lower

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in anteroposterior radiation. The authors indicated that the anterior field may be preferred mainly in anterior mediastinal and neck involvement, but that more studies are required.

Long term side effects of treatments have been questioned, especially in Hodgkin's lymphoma, which is nowadays considered a cure disease. As can be seen from the above studies, ischemic heart disease and second cancer that may develop years after Hodgkin's lymphoma treatment. To reduce these risks different radiotherapy techniques are applied according to the location of the disease. For this purpose, in three studies in 2017 ASTRO, it was predicted that only anterior field or anterio-posterior radiation technique could reduce these side effects in the long term. In our clinic, only anterior field or anterior posterior radiotherapy was applied for a period. We retrospectively reviewed all patients (113 patient) who had been treated with Hodgkin's disease for a period of time with these treatment techniques and investigated the long-term efficacy and side effects of these methods.

In light of the above information, we re-evaluated a total of 113 patients who had received radiotherapy and/or chemotherapy for stage I-II disease out of 320 patients with Hodgkin's lymphoma who presented to and were treated at the Okmeydanı Training and Research Hospital Radiation Oncology Clinic between January 1974 and December 1997, and who then continued regular follow-up. Forty two patients (group 1) had been treated with only anterior field radiation using 8-MV photon bolus and/or treatment was completed using electron therapy in case of the presence of missing dose in the superficial lymph nodes; 71 patients (group 2) had been treated with anteroposterior field radiation. The patients were retrospectively investigated for secondary malignancies, cardiac diseases, and to compare the two radiotherapy methods in addition to evaluating general supradiaphragmatic stage I-II Hodgkin's lymphoma.

METHODS

We retrospective re-evaluated a total of 113 patients (all) who had received radiotherapy and/or chemotherapy for stage I-II disease out of 320 patients with Hodgkin's lymphoma who presented to and were treated at the Okmeydanı Training and Research Hospital Radiation Oncology Clinic between January 1974 and December 1997, and who then continued regular follow- up. In this period, our radiotherapy technique used which only anterior mantle and anterior-posterior mantle treatment with and/or chemoterapy, were evaluated for long-term side effects and efficacy. For a better evaluation of the follow-up, 10-year results were given primarily in these patients. We investigated the distribution characteristics, staging and treatment methods, recurrence regions and rates, survival times in accordance with group, and treatment type in detail, seconder malignancies and ischemic heart disease. Only anterior field mantle using bolus with 8-MV photon to 42 patients (group 1), while 71 patients (group 2) received anterior posterior field mantle 8-MV photon therapy.

If there is a lack of dose from the anterior area, it is completed by electron boost. Mean radiotherapy doses is 36 Gy/180-200 cGy daily.

Given the retrospective design of the study, informed consent and ethics committee approval were not obtained. This article complies with the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association Declaration of Helsinki.

Statistical Analysis

Patient data collected in the scope of the study were analyzed with the SPSS for Windows 21.0 package program. For discrete data, frequency and percentage were given as descriptive values. Kaplan-Meier method was used for survival analysis. "Chi-square test" was used to compare two discrete groups. Results were considered statistically significant when p value was less than 0.05.

The Kaplan-Meier method was used for survival analysis, and significance was evaluated using the chi-square test (4).

RESULTS

For the years we included in the study, the shortest patient follow-up was 36 months and the longest was 285 months. But long-term follow-up is 581 months and median overall survival (OS) was 30 years. Pretreatment patient and tumor characteristics are presented in Table 1. The disease free survi for group 1 patients with a complete response at 10 years were 62% [95% confidence interval (CI): 58-66], for group 2 patients were 60% (95% CI: 56-64). Progression free survival at 10 years for group 1 was 59% (95% CI: 55-63), group 2 was 58% (95% CI:54-62). The median age in group 1 and group 2 was 33 years and 34 years, respectively. Distribution of the statistical analysis are showed Table 2. Rates of chemotherapy administration by stages is presented in Table 3.

The secondary malignancies detected were lung cancer (3 patients), hemangiosarcoma (1 patient), larynx carcinoma (1 patient), neurofibromatosis (1 patient), and thyroid carcinoma (1 patient). Breast cancer and ischemic heart disease were not detected during the study period.

Kaplan-Meier survival curve for all patients is shown in Figure 1.

In group 1, the 5-year and 10-year survival rate was 77.18% (95% CI: 73-81) and 70.88% (95% 66-75), respectively. Kaplan-Meier survival curve for group 1 is shown in Figure 2.

In group 2, the 5-year and 10-year survival rate was 71.33% (95% 67-76) and 67% (95% 63-71), respectively. Kaplan-Meier survival curve for group 1 is shown in Figure 3.

All groups 30 years survival 60% (95% CI: 56-64) (group 1 61.5%, group 2 58.5%).

Table 1. Patient characteristics		
Characteristics	**n**	**%**
Group		
Group 1	42	37.2
Group 2	71	62.8
Gender		
Male	63	55.8
Female	50	44.2
Histology		
L. rich	28	24.8
Nodular	32	28.3
Mixed	50	44.2
L. poor	3	2.7
Stage		
IA	26	23.0
IB	8	7.1
IIA	34	30.1
IIB	45	39.8
Subtotal nodal irradiation		
Positive	40	35.4
Negative	73	64.6
Recurrence		
Yes	35	31.0
No	78	69.0
Mortality		
Alive	91	80.5
Deceased	22	19.5

No statistical difference was detected for both groups.

Statistical note: In addition, the detailed mean and median survival values of the subgroups were not included for this disease, which was cured in parallel with current developments since it was beyond the primary purpose of the study.

Table 2. Shows the distribution of the statistical					
Gender	**Group 1**		**Group 2**		**p value**
Male	24	57.1	39	54.9	0.843*
Female	18	42.9	32	45.1	
p value	0.235**		0.189**		
Histology					
L. rich	8	19.0	20	28.2	0.177**
Nodular	10	23.8	22	31.0	
Mixed	23	54.8	27	38.0	
L. poor	1	2.4	2	2.8	
p value	0.192**		0.345**		
Stage					
IA	11	26.2	15	21.1	0.106**
IB	2	4.8	6	8.5	
IIA	14	33.3	20	28.2	
IIB	15	35.7	30	42.3	
p value	0.155**		0.148**		
Subtotal nodal irradiation					
Negative	25	59.5	48	67.6	0.655*
Positive	17	40.5	23	32.4	
Recurrence					
No	27	64.3	51	71.8	0.554*
Yes	15	35.7	20	28.2	
Recurrence, specify					
No	27	64.3	51	71.8	0.349**
Internal	2	4.8	11	15.5	
External	13	31.0	9	12.7	
Survival					
Alive	36	85.7	55	77.5	0.285*
Deceased	6	14.3	16	22.5	
*Fisher exact test, **Pearson chi-square test					

Table 3. Shows the rates of chemotherapy administration									
Group 1	**IA**		**IB**		**IIA**		**IIB**		**p value**
Did not receive	8	72.7			10	71.4			0.000*
Received	3	27.3	2	100	4	28.6	15	100.0	
Group 2	**IA**		**IB**		**IIA**		**IIB**		**p value**
Did not receive	13	86.7	3	50.0	7	35.0	1	3.3	0.000*
Received	2	13.3	3	50.0	13	65.0	29	96.7	
*p<0.05; Pearson chi-square									

DISCUSSION

This study with long-term results showed that the risk of ischemic heart disease, second solid cancer risks did not change profound among patients with Hodgkin's lymphoma who were treated.

In the present study, the male:female ratio was 1.26, which is statistically compatible with the rate of 1.26 in the literature (5,6).

Here, the median age was 34 years; however, it is 26 years in the literature. This inconsistency stems from the transfer of pediatric patients to another center for treatment.

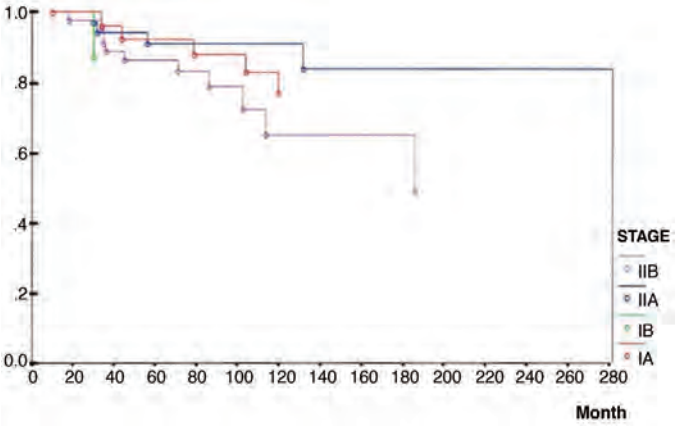

Figure 1. Kaplan-Meier survival curve for all patients

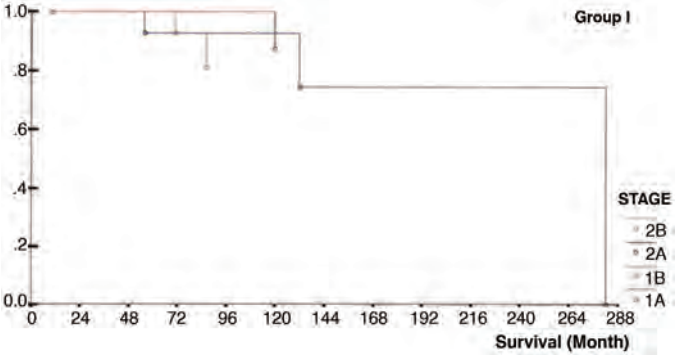

Figure 2. Kaplan-Meier survival curve gor group I

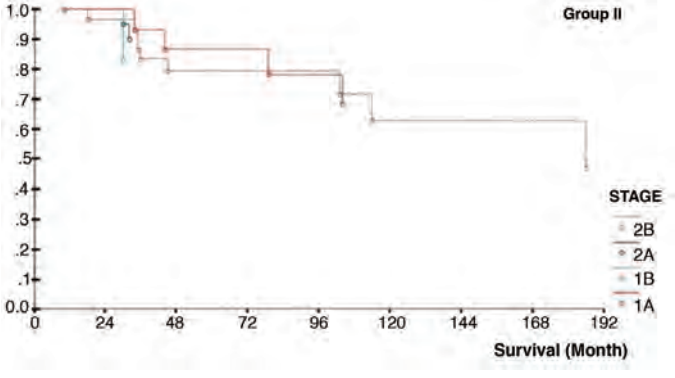

Figure 3. Kaplan-Meier survival curve for group II

There was a greater proportion of an obvious mixed type histology in the patients included in our study; however, nodular sclerosing histology was the most frequently detected histologic type in the literature (5,7). One reason is that cases that did not fit the other histologic types tended to be included in the mixed type. The most important reason is that, compared with the other histologic types, etiologic association between the mixed type with infection agents is more frequently detected in Turkey as compared the developing countries. In particular, the development of this histologic type has been attributed to Epstein-Barr virus infection (5,8-12).

In the present series, both groups had similar survival rates. The 5-year survival rate for stage IA and stage IIA disease in group 1 was 83.3% and 68.1%, respectively; the respective 10-year survival rates were 77.78% and 58.92%, respectively. In group 2, the 5-year survival rates were 90% and 61.9%, respectively, and that for 10-year survival was 89.74% and 67.6%, respectively. These results are statistically compatible with the literature, and we suggest that the difference between the 5-year and 10-year survival is due to the recognition of the total 5 patients as exitus from both groups after initially presenting as controls in the first 5 years; however, they then did not show up in the controls.

In group 1, the 5-year survival rate for stage IB and stage IIB disease was 100% and 81.47%, respectively, and that for 10-year survival was 100% and 76.47%, respectively. In group 2, the 5-year survival rate was 83.3% and 84.46%, respectively, and that for 10-year survival was 81.62% and 47.45%, respectively. There is no difference in disease-free survival and OS between both radiotherapy techniques.

Secondary malignancies may be detected in the long-term follow-up of Hodgkin's lymphoma, including in particular leukemia, non-Hodgkin's lymphoma, and solid tumors. The risk of leukemia and lung cancer is increased 3-7 years after treatment in patients who receive an alkylene agent and procarbazine (mechlorethamine, vincristine, procarbazine, prednisone) (13,14). Secondary solid tumors are more frequently detected due to radiotherapy (14), and generally develop after 7-10 years. The most frequently detected malignancies are lung, breast, and gastrointestinal malignancies (15-17).

In the present series, secondary primary tumors were detected in the form of 3 lung carcinomas in both groups (group 1, 2 patient; group 2, 1 patients), hemangiosarcoma in 1 patient (group 2), larynx carcinoma in 1 patient (group 1), neurofibromatosis in 1 patient (group 2), and thyroid carcinoma in 1 patient (group 1). Interestingly, we detected

no breast cancer during our study period, which is suggested to be associated mainly with the procarbazine chemotherapy administered in that period (18-26). However, long-term follow-up after the study detected breast cancer in 1 patient, and heart attack due to coronary artery disease in 2 patients. The death of the younger patient was associated with the disease.

CONCLUSION

We discuss the patients' quality of life in addition to the possible late adverse effects of the treatments given the increased curability and survival in Hodgkin's lymphoma. The aim is to minimize the treatment-related adverse effects, given patients' longer life expectancy. For this reason, it is currently being tried to improve the quality of life and survival by reducing the risk of organs and heart doses in terms of secondary cancer such as lung and breast, ischemic heart disease by different methods such as anterior field radiotherapy. Treatment fields must be minimized as far as possible with guidelines using current modern radiotherapy techniques.

In our study, the incidence of ischemic heart disease, especially in patients with anterior mediastinal localized Hodgkin lymphoma, can be a protective factor for single anteror field radiotherapy. However, attention should be paid in terms of breast cancer in women. Anterio-posterior radiotherapy can also be used in patients at risk of lung cancer, since fields receiving high volumetric doses will decrease. But still, giving up smoking and increasing physical activities must be recommended, particularly against lung cancer and ischemic heart disease. Patients receiving treatment for Hodgkin's lymphoma must have regular heart and breast controls.

Ethics

Ethics Committee Approval: This article complies with the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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OPEN ACCESS

Asymmetric Dimethylarginine Level as an Indicator for Cardiovascular Risk in Patients with Metabolic Syndrome

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Abstract

Objective: This study aimed to make an early diagnosis of endothelial dysfunction, the initial pathology of atherosclerosis in metabolic syndrome (MS) patients, and to investigate the usefulness of serum asymmetric dimethylarginine (ADMA) levels as a marker of cardiovascular risk.

Methods: Thirty-eight patients (24 women and 14 men) who were diagnosed with MS, according to the National Cholesterol Education Program Adult Treatment Panel III, were included in the study. Patients with a history of systemic diseases, except components of MS, and smokers were excluded from the study. The control group comprised 25 and 12 healthy women and men, respectively; with similar age profiles. Serum ADMA levels and carotid intima-media thickness (CIMT) were measured in patients and controls.

Results: Lower serum ADMA levels and higher CIMT measurements were observed in the patient group than in the control group ($p<0.001$ and $p<0.001$, respectively). C-reactive protein (CRP) was significantly higher in patients than in controls ($p<0.001$). Correlation analysis revealed a significant and inverse correlation between plasma ADMA concentrations and fasting blood glucose ($p<0.001$, $r=-0.421$), HbA1c ($p=0.001$, $r=-0.361$), CRP ($p=0.003$, $r=-0.335$), and CIMT measurements ($p=0.024$, $r=-0.261$). Among the patients with MS, 32 were diagnosed with type 2 DM; among whom 29 were receiving metformin treatment. ADMA levels in MS patients with and without metformin therapy were 4.5 ± 1.7 nmol/mL and 7.3 ± 1.2 nmol/mL, respectively; and the ADMA levels were significantly lower in the former than in the latter ($p=0.007$).

Conclusion: MS is a cluster of diseases in which pro-atherosclerotic processes such as DM, hypertension, obesity, and hypercholesterolemia coexist. In our study, when increased CIMT values were considered as evidence for the presence of atherosclerosis in patients, the low serum ADMA levels may be related to metformin therapy, poor glycemic control, and/or problems in the immune-assay.

Keywords: Metabolic syndrome, ADMA, CIMT, atherosclerosis

INTRODUCTION

Significant features of metabolic syndrome (MS) include central obesity, hypertension, dyslipidemia, glucose intolerance, vascular inflammation, and prothrombotic condition (1). Studies have highlighted the effect of insulin resistance on MS components and its critical role in the pathophysiology of MS (2). Insulin resistance may lead to hypertension, dyslipidemia, coagulation abnormality, endothelial dysfunction, and cardiovascular diseases (1).

Endothelial dysfunction is the earliest evidence of coronary artery disease and its occurrence in the early stages of the disease; before atheroma plaque formation. The main indicator of endothelial dysfunction is the disruption of endothelium-dependent vasodilatation caused by nitric oxide (NO). NO

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is synthesized from L-arginine by NO synthase (NOS). NO produced in the endothelium, affects vascular tone and leads to vasodilatation (3,4).

L-arginine is methylated with intracellular methyltransferases and converted to asymmetric dimethylarginine (ADMA), the metabolite of methylated L-arginine. Since, ADMA is an endogenous competitive inhibitor of NOS; it is an important risk predictor for cardiovascular disease; as a marker of endothelial dysfunction (5).

Studies have revealed that in sudden deaths secondary to coronary artery disease, the development of atherosclerosis was not limited to the coronary arteries alone. Therefore, ultrasonographically measured carotid intima-media thickness (CIMT) may be used to detect the presence of atherosclerotic plaques, degree of calcification, arterial lumen diameters, and asymptomatic atherosclerotic disease (6).

In this study, endothelial dysfunction and increased cardiovascular risk in MS were evaluated with serum ADMA levels and CIMT that are considered to be risk factors for cardiovascular disease. The aim of this study was to make an early diagnosis of endothelial dysfunction, the initial pathology of atherosclerosis in MS patients, and to investigate the usefulness of serum ADMA levels as a marker of cardiovascular risk.

METHODS

Study Population

This study was performed prospectively in patients followed in internal medicine, and/or endocrinology and metabolism disease clinics of Bursa Yüksek İhtisas Training and Research Hospital from which the ethics committee approval is obtained (23.10.2013/3). For the diagnosis of MS, according to the National Cholesterol Education Program Adult Treatment Panel III criteria, at least three of the following criteria were required:

- Fasting blood glucose (FBG) >110 mg/dL
- Triglyceride (TG) >150 mg/dL
- Waist circumference >88 cm for women, >102 cm for men
- High-density lipoprotein (HDL) cholesterol <50 mg/dL in women and <40 mg/dL in men
- Blood pressure >130/85 mmHg

Results of hematological investigations were obtained from the archived files of patients. Waist circumferences and body mass indices of patients (BMI) were calculated at the time of their inclusion in the study. ADMA and CIMT were assessed prospectively.

Laboratory Methods

Venous blood samples for serum ADMA level measurements were taken in the morning, following a 12-hour fasting period. They were transported to the laboratory in ice molds and centrifuged at 4000 rpm for 5 min and stored at -80 °C. ADMA measurements were carried out with AD double-antibody sandwich ELISA method with Human ADMA ELISA Kit (Sunred Biological Technology, Shanghai China), with a sensitivity range of 0.05-15 nmol/mL, in the Biochemical Laboratory of Bursa Yüksek İhtisas Training and Research Hospital.

Carotid Intima-media Thickness

CIMT measurements were performed for patient group and control group using Logiq 5 Pro (GE Healthcare, Milwaukee, USA) ultrasound, using a 7.5 MHz linear array transducer. For CIMT, three measurements were taken from approximately 1 cm proximal to the bifurcation of both main carotid arteries, when the anterior and posterior walls were seen bilaterally. The arithmetic mean of the three measured values of the randomly selected region was used.

Statistical Analysis

Average, standard deviation, median, lowest, highest, frequency, and ratio values were used for descriptive statistics. The distribution of variables was assessed with the Kolmogorov-Smirnov test. Mann-Whitney U test and independent sample t-test were used in the analysis of quantitative data, while χ^2 test was used for qualitative data. Spearman correlation analysis was used for evaluating correlation. Statistical analysis of the data was performed with "SPSS for Windows, Version 22." The data were represented by mean ± standard deviation, and $p < 0.05$ was considered as statistically significant.

RESULTS

Thirty-eight patients with MS (24 women and 14 men) and 37 healthy controls (25 women and 12 men) were included in the study, with median ages of 45.1±8.3 years (range; 30-59 years) and 41.4±8.0 years (range; 31-60 years), respectively. The median FBG and HbA1c levels were 167 mg/dL (96-280 mg/dL) and 9% (5.6-13%); and 88 mg/dL (73-113 mg/dL) and 5.5% (4.8±5.8%); in MS and control groups, respectively. The median TG and HDL cholesterol levels were 269 mg/dL (115-480 mg/dL) and 39 mg/dL (22-63 mg/dL); and 112 mg/dL (57-198 mg/dL) and 45 mg/dL (21-84 mg/dL); in MS and control groups, respectively. The median waist circumferences in MS and control groups were 110

cm (104-220 cm) and 65 cm (60-78 cm), respectively; while the median systolic and diastolic blood pressure (SBP and DBP) were 130 mmHg (120-150 mmHg) and 80 mmHg (75-90 mmHg) in the MS group and 120 mmHg (100-128 mmHg) and 75 mmHg (60-80 mmHg) in control group (Table 1).

The serum ADMA levels were significantly different between MS and control groups (5.1±1.9 nmol/mL and 7.7±3.3 nmol/mL, respectively; p<0.001). The same was true for CIMT measurements (0.07±0.01 mm and 0.05±0.01 mm, respectively; p<0.001) (Table 2) (Figure 1, 2).

In MS group, statistically significant negative correlations were observed between serum ADMA levels and (BMI) (r=-0.428; p=<0.001), waist circumference (r=-0.351; p=0.002), SBP (r=-0.330; p=0.004), FBG (r=-0.421; p=<0.001), HbA1c (r=-0.361; p=0.001), TG (r=-0.316; p=0.006), CRP (r=-0.335; p=0.003), and CIMT (r=-0.261; p=0.024). There was a positive correlation between serum ADMA levels and HDL cholesterol (r=0.247; p=0.033) (Table 3).

Further, statistically significant positive correlations were observed between CIMT values and BMI (r=0.713; p=<0.001), waist circumference (r=0.661; p=<0.001), SBP (r=0.610; p=<0.001), FBG (r=0.711; p=<0.001), HbA1c (r=0.686; p=<0.001), TG (r=0.502; p=<0.001), and CRP (r=0.402; p=<0.001). There was a negative correlation between CIMT values and HDL cholesterol (r=-0.279; p=0.015) (Table 4).

Thirty-two of the patients with MS were diagnosed with type 2 DM, and 29 of these were receiving metformin treatment. ADMA levels in MS patients with and without metformin therapy were 4.5±1.7 nmol/mL and 7.3±1.2 nmol/mL, respectively. ADMA levels were significantly lower in patients with MS receiving metformin than in patients without metformin (p=0.007).

Table 1. Demographic and biochemical features of the patients

Variables	MS group		Control group		p
	Mean ± SD	Med (Min-Max)	Mean ± SD	Med (Min-Max)	
Age (years)	45±8.3	46 (30-59)	41.4±8.0	42 (31-60)	NS
Weight (kg)	101.6±12.8	98 (83-15)	67.2±4.8	65 (60-80)	<0.001
BMI (kg/m²)	36.6±4.2	36 (31-46)	23.2±1.2	24 (20-25)	<0.001
Ws C. (cm)	114.0±18.9	110 (104-220)	66.8±4.9	65 (60-78)	<0.001
SBP (mmHg)	132.1±7.3	130 (120-150)	116.4±6.8	120 (100-128)	<0.001
DBP (mmHg)	82.5±4.8	80 (75-90)	74.6±5.9	75 (60-80)	<0.001
FBG (mg/dL)	165.8±50.1	167 (96-280)	87.8±8.1	88 (73-113)	<0.001
BUN (mg/dL)	13.8±3.6	13 (6.0-25.0)	12.1±4	12 (5.0±24)	NS
Creatinin (mg/dL)	0.7±0.2	0.7 (0.1-1.0)	0.8±0.1	0.8 (0.6-1.0)	NS
Tot C (mg/dL)	227.4±43.7	223 (138-356)	201.0±43.1	199 (114-300)	0.010
LDL-C (mg/dL)	137.8±65.2	130 (51-450)	124.8±36.5	124 (61-205)	NS
HDL-C (mg/dL)	39.1±8.8	39 (22-63)	46.9±11.8	45 (21-84)	0.001
TG (mg/dL)	275.8±100	269 (115-480)	136.5±74.6	112 (57-198)	<0.001
AST (IU/L)	25.4±12.9	21 (12-70)	21.1±4.0	12 (5-24)	NS
ALT (IU/L)	26.7±13.5	24 (9-64)	20.8±10.4	17 (8-45)	0.036
Uric acid (mg/dL)	4.8±1.0	4.9 (2.7-6.6)	4.9±1.5	4.8 (2.2±7.5)	NS
HbA1c (%)	8.7±2.1	9 (5.6-13)	5.5±0.2	5.5 (4.8±5.8)	<0.001
CRP (mg/dL)	8.1±5	6.3 (3.4-21)	4.5±2	3.4 (3.3-11)	<0.001

SD: Standard deviation, Min: Minimum, Max: Maximum, Med: Median, NS: Non-significant, BMI: Body-mass index, Ws C: Waist circumference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, BUN: Blood urea nitrogen, Tot C: Total cholesterol, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, TG: Triglycerides, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, MS: Metabolic syndrome

Table 2. Carotid intima media thickness and asymmetric dimethylarginine levels in metabolic syndrome and control groups

	MS group (mean ± SD)	Control group (mean ± SD)	p
CIMT (mm)	0.07±0.01	0.05±0.01	<0.001
ADMA (nmol/mL)	5.1±1.9	7.7±3.3	<0.001

SD: Standard deviation, CIMT: Carotid intima media thickness, ADMA: Asymmetric dimethylarginine

DISCUSSION

In the present study, serum ADMA levels and CIMT measurements were compared between MS patients; a risk group for atherosclerosis, and healthy controls.

Some studies have focused on the relationship between serum ADMA levels and atherosclerosis. Vallance et al. (7) were the first to demonstrate that endogenous ADMA antagonizes endothelium-induced vasodilatation. They reported elevated plasma ADMA levels in patients with endothelial dysfunction, and considered it as a risk factor for atherosclerosis. Böger et al. (8) described ADMA as a new cardiovascular risk factor and found that plasma ADMA levels were higher in patients with hypercholesterolemia than in healthy controls. Further, Cooke (9) reported that serum ADMA levels were associated with the development of cardiovascular diseases such as endothelial dysfunction, hypercholesterolemia, peripheral vascular disease, and hypertension.

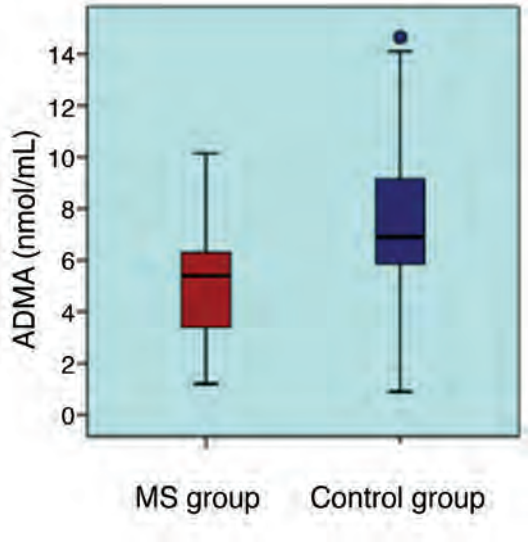

Figure 1. Serum asymmetric dimethylarginine levels
ADMA: Asymmetric dimethylarginine, MS: Metabolic syndrome

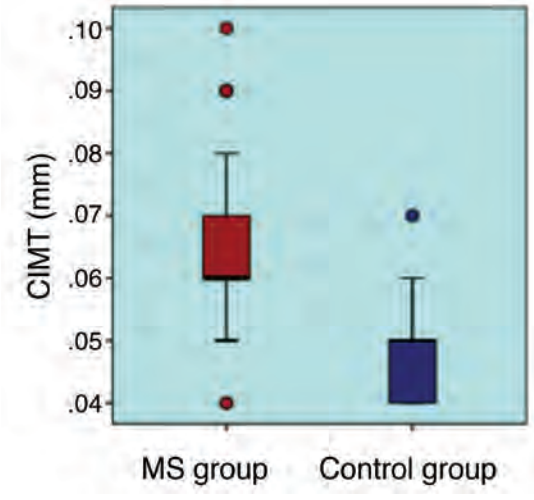

Figure 2. Carotid intima media thickness in groups
CIMT: Carotid intima media thickness, MS: Metabolic syndrome

Many studies have reported increased plasma ADMA concentrations in type 1 and type 2 diabetic patients. In a study of 40 uncomplicated type 1 diabetic patients, plasma ADMA levels were increased before the development of vascular complications (10). Another study, including 408 patients with type 1 diabetic nephropathy, suggested that increased ADMA levels contributed to diabetes-induced organ damage (11). However, there are other studies with contradicting results. In a population-based Framingham offspring study by Böger et al. (12), the mean ADMA levels were similar in diabetic and non-diabetic groups. Although, there was a positive correlation between ADMA levels and mortality in the non-diabetic group, no significant relationship was observed in the diabetic group. Päivä et al. (13) found decreased ADMA levels in type 2 diabetic patients and argued that this result may be due to increased glomerular filtration rate and poor glycemic control in their patients. In another study by Onat et al. (14), the relationships between serum ADMA levels and MS, type 2 DM, and coronary artery disease were investigated in 848 patients. Contrary to the expectations, serum ADMA levels were found to be low in patients with high fasting glucose, and they believed that this may be due to the leakage of some ADMA proteins, triggering an autoimmune response during the immune assays. In the study of Xiong et al. (15), it was found that adopting measures to target various metabolic abnormalities of MS and insulin-sensitizing treatments, generally decreased ADMA levels. Wang et al. (5) found a decrease in plasma ADMA levels and improved flow-mediated dilatation of the brachial artery, 8 weeks after treatment, with rosiglitazone in non-diabetic patients with MS. A recent study found that plasma ADMA levels had a dynamic balance and that they did not correlate with cellular levels (16).

In our study, when compared with healthy controls, serum ADMA levels were found to be significantly lower and CIMT was found to be significantly higher, in patients. In our study, 86% of the patients in the MS group were diabetic, the median HbA1c levels were 9% (5.6-13%), and 29 patients received metformin. Serum ADMA levels were significantly lower in the metformin group than in the non-metformin group. In light of these findings, poor glycemic control-related interference or the use of metformin to break down insulin resistance may be one of the causes of low serum ADMA levels in the MS group.

Table 3. The correlations between asymmetric dimethylarginine and metabolic syndrome components

		Age	BMI	Ws C	SBP	DBP	CRP	CIMT
ADMA	r	-0.112	-0.428	-0.351	-0.330	-0.217	-0.335	-0.261
	p	0.337	<0.001	0.002	0.004	0.062	0.003	0.024
		FBG	**HbA1c**	**Tot C**	**LDL-C**	**HDL-C**	**TG**	
ADMA	r	-0.421	-0.361	0.017	0.155	0.247	-0.316	
	p	<0.001	0.001	0.884	0.186	0.033	0.006	

ADMA: Asymmetric dimethylarginine, BMI: Body-mass index, Ws C: Waist circumference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CRP: C-reactive protein, CIMT: Carotid intima media thickness, FBG: Fasting blood glucose, Tot C: Total cholesterol, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, TG: Triglycerides

Table 4. The correlations between carotid intima media thickness and metabolic syndrome components

		Age	BMI	Ws C	SBP	DBP	CRP
CIMT	r	0.431	0.713	0.661	0.610	0.512	0.402
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
		FBG	**HbA1c**	**Tot C**	**LDL-C**	**HDL-C**	**TG**
CIMT	r	0.711	0.686	0.235	0.082	-0.279	0.502
	p	<0.001	<0.001	0.043	0.486	0.015	<0.001

BMI: Body-mass index, Ws C: Waist circumference, SBP; systolic blood pressure, DBP: Diastolic blood pressure, CRP: C-reactive protein, FBG: Fasting blood glucose, Tot C: Total cholesterol, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, TG: Triglycerides, CIMT: Carotid intima media thickness

There are several limitations to our study. The first was the inadequate number of participants in the patient and control groups. Another was that most patients in the MS group had a diagnosis of DM and were receiving treatment for the same. If the newly diagnosed patients, who had no apparent DM and were not receiving any medications, were included in the study, the relationship between MS and serum ADMA could be considered to be free from medication effects and possible effects of poor glycemic control. Other limitations were the lack of insulin values and the absence of objective insulin resistance, although patients met the MS criteria.

CONCLUSION

In conclusion, in many studies, CIMT is accepted as an indicator of generalized atherosclerosis including that of the coronary arteries. MS is a cluster of diseases in which pro-atherosclerotic processes such as DM, hypertension, obesity, and hypercholesterolemia coexist. In our study, when increased CIMT values were considered as evidence for the presence of atherosclerosis in patients, the low levels of serum ADMA may be related to metformin therapy, poor glycemic control, and/or problems in the immune-assay.

Ethics

Ethics Committee Approval: Bursa Yüksek İhtisas Training and Research Hospital from which the ethics committee approval is obtained (23.10.2013/3).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., A.K., Concept: S.A., S.K., G.K., Design: S.A., A.K., G.K., Data Collection or Processing: S.A., A.K., Analysis or Interpretation: S.A., S.K., Literature Search: S.A., A.K., Writing: S.A.

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The Effect of Surgical Timing on the Outcomes of Pediatric Gartland Type III Supracondylar Humeral Fractures

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Abstract

Objective: In this study,we aimed to evaluate the effect of surgical treatment timing of Gartland extension type III humeral fractures on functional and cosmetic outcomes, in the pediatric age group and to compare them with literature.

Methods: Between November 2015 and October 2018, files of patients who were admitted to the emergency orthopedics department with Gartlantd extension type III supracondylar humeral fractures and who underwent surgery were investigated. Fifty cases under the age of 15 years were included in the study. These patients were divided into two groups (early and late groups) by examining time before surgery. At outpatient follow up, functional and cosmetic results were evaluated using Flynn criteria at the 12th postoperative week.

Results: Fifty patients (58% males and 42% females) with an average age of 79.7 months (range=15-164 months) were included in the study. All of the patients had closed fractures. Surgical open reduction rate was 30% (n=15), with 20% (n=5) in the early group and 40% (n=10) in the late group. Patients were evaluated according to Flynn criteria at the 12th week of outpatient follow up. In the early group, 92% (n=23) and 8% (n=2) of patients had excellent and good cosmetic results, respectively; 64% (n=16), 28% (n=7), 4% (n=1), and 4% (n=1) had excellent, good, moderate, and poor functional results, respectively. When the outpatient clinic records of the late group patients were examined, 88% (n=22) and 12% (n=3) had excellent and good cosmetic results, respctively, and 52% (n=13), 24% (n=3), 16% (n=4), and 8% (n=2) had excellent, good, moderate, and poor functional results, respectively. No significant difference was found between the two groups in terms of cosmetic and functional results (p=0.641 and p=0.260, respectively). However, it was observed that patients operated with a closed method had better functional outcome than those treated by open surgery (p<0.001).

Conclusion: There was no significant difference between the early and late groups in terms of cosmetic and functional durations of the cases. However, we identified that early surgical treatment reduces operative time, C-arm fluoroscopy usage, hospitalization, and open surgery ratio. We propose that Gartland type III supracondylar humeral fractures should be treated with closed surgical methods within the first 12 hours considering the negative effect of open reduction on functional outcomes.

Keywords: Pediatric humeral fractures, supracondylar humeral fractures, timing of surgery, Flynn criteria

INTRODUCTION

The second most common fracture seen in the pediatric age group is the supracondylar humeral fracture. It constitutes approximately 50% of fractures around the elbow (1). These type of fractures are usually seen in the left upper extremity of boys aged 5-6 years (2). According to the Gartland classification, approximately 97-99% of these fractures are extension types. The injury mechanism is falling on an open hand when the elbow extended. In such fractures, the proximity of the neurovascular structures in the antecubital region to the fracture site increases the risk of direct injury and the risk of indirect damage due to pressure caused by the hematoma.

The aim of the treatment of pediatric supracondylar humeral fractures is to allow elbow movement as soon as possible. Treatment options range from closed reduction and plaster fixation to open surgery. According to Gartland classification,

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extension type III fractures should be treated surgically, because they are unstable with a risk of damage to neurovascular structures (3). In surgical practice, closed reduction and percutaneous pinning (CRPP) are the gold standard of surgical treatment. In cases where closed surgery is not enough to achieve anatomical reduction, switching to open surgery should be considered (4).

Complications of open or closed surgical treatment include pin-track infections, iatrogenic neurovascular injury, cubitus varus, hyperextension deformities (4).

In this study, we aimed to evaluate the effect of surgical treatment timing applied to Gartland extension type III humerus fractures in the pediatric age group on the functional and cosmetic outcomes determined using Flynn criteria and to compare them with literature.

METHODS

After approval from the local ethics committee (Okmeydanı Training and Research Hospital 06.02.2018-827), medical records of patients admitted to our emergency orthopedics department, with the diagnosis of Gartland type III supracondylar humeral fracture were obtained. Those who had undergone surgery were included in our study. Informed consent was obtained from all individual participants. Fifty cases under the age of 15 years were included in the study. Patients were divided into two groups: early group (those operated in the first 12 hours after trauma) and the late group (those operated after 12 hours). Both groups consisted of 25 patients.

The age, gender, fracture side, time to surgery, open or closed surgical treatment, use of C-arm floroscopy, incision site of the patients who underwent open reduction and hospitalization time were recorded.

Functional and cosmetic outcomes of the patients were determined using the Flynn criteria (5) (Table1) with face-to-face interview at a 12 weeks postsurgery outpatient clinic follow-up visit. Patients were followed up with k-wire dressings, withdrawal of the wires based on radiological fracture healing findings, and the duration was recorded. Early complications such as pin tract or wound infection were investigated.

Inclusion criteria;

- Patients under 15 years,
- Gartland type III supracondylar humeral fractures,
- Surgically treated patients,
- Available hospitalization and outpatient clinic records.

Exclusion criteria;

- Open fractures,
- Patients with second fractures of the same extremity,
- Fractures with neurovascular deficit were not included in the study.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) 21.0 and Microsoft Office Excel 2016 programs were used for statistical analysis. Shapiro-Wilk test was used to determine whether the study findings were in normal distribution. Comparisons between groups was done using independent t-test or analysis of variance. The Mann-Whitney U test was used for the non-parametric data. All statistical tests were two-sided and statistical significance was set at p=0.05. The results were analyzed on a 95% confidence interval basis.

RESULTS

There were 29 males (58%) and 21 females (42%) in the study. The mean age was 79.7±43.6 months (range=15-164 months). Sixteen of the cases were right sided fractures. No statistically significant difference was found between the two groups as regards gender distribution, age, and fracture sides (Table 2).

All patients received premedication by anesthesists under emergency conditions before operation. Patients in the early group were operated within the first 12 hours and the mean time was 7.08±1.8 hours. Patients in the late group were operated after at least 12 hours of admission and the mean time was recorded as 21.8±4.5 hours. The mean postoperative duration of hospitalization was 1.8±0.4 days in the early group and it was 2.7±1.3 days in the late group. The hospitalization period of the patients who were operated in the early period

Table 1. Flynn criteria (5)

	Cosmetic	Functional
	Carrying angle loss (°)	Total ROM of elbow loss (°)
Satisfactory		
Excellent	0-5	0-5
Good	6-10	6-10
Fair	11-15	11-15
Unsatisfactory		
Poor	>15	>15

ROM: Range of motion

was statistically significantly shorter than those in the late group (p=0.002) (Table 2).

All patients were operated by the same surgical team. The mean duration of surgery was 36.4±14.4 minutes in the early group and 58.2±23.1 minutes in the late group. When the C-arm fluoroscopy usage times during the operation were examined, it was 10.9±1.8 seconds in the early group and 22.3±2.2 seconds in the late group. Operation and C-arm fluoroscopy usage times were significantly lower in the early group (p <0.001) (Table 2).

Open surgical reduction ratio was 30% (n=15) in all patients. Five of these patients were in the early group, 3 were operated by lateral incision, and 2 were operated by lateral and medial approaches. The remaining 10 patients were part of the late group. Four of them were operated by lateral and the others by lateral and medial approaches. There was no statistically significant difference between the groups in terms of surgical reduction method (p=0.127). However, patients treated by closed surgery had significantly lower age, hospitalization, and operation times than those treated by open surgery (p<0.001) (Table 3). In addition, it was observed that patients operated with closed method had better functional outcome than those treated by open surgery (p<0.001) (Figure 1). None of the patients had neurovascular complications in the early postoperative period. The mean duration of pin removal was 7.1±0.9 weeks in the early group and 6.9±0.8 weeks in the late group. No statistically significant difference was observed between both groups in terms of pin removal times (p=0.777). In the outpatient follow up, only one patient had superficial pin-track infection and was treated with oral antibiotherapy.

Patients were evaluated according to Flynn criteria at the 12th week of outpatient follow up. In the early group, 92% (n=23) and 8% (n=2) of patients had excellent and good cosmetic results, respectively; 64% (n=16), 28% (n=7), 4% (n=1), and 4% (n=1) had excellent, good, moderate, and poor functional results, respectively. When the outpatient clinic records of the late group patients were examined, 88% (n=22) and 12% (n=3) had excellent and good cosmetic results, respctively, and 52% (n=13), 24% (n=3), 16% (n=4), and 8% (n=2) had excellent, good, moderate, and poor functional results, respectively. No significant difference was found between the two groups in terms of cosmetic and functional results (p=0.641 and p=0.260, respectively).

Table 2. Demographic data of patients

	Early group	Late group	p values	1-β values
Gender			0.77*	
Female **Male**	10 (20%) 15 (30%)	11 (22%) 14 (28%)		
Age (months)	68±28.8	90±53	0.08**	
Side **Right** **Left**	 9 (18%) 16 (32%)	 7 (14%) 18 (36%)	 0.54**	
Admission peirod (day)	1.8±0.4	2.7±1.3	0.002	91%
Surgery time (minute)	36.4±14.4	58.2±23.1	<0.001	98%
C-arm fluoroscopy usage time (second)	10.9±1.8	22.3±2.2	<0.001	99%

*Mann-Whitney U test, **Student t-test

Table 3. Comparison of patients between surgical reduction groups

	Closed surgery	Open surgery	p values	1-β values
Age (months)	68±39.8	109±36.8	<0.001	97%
Admission peirod (day)	1.9±0.5	3±1.6	<0.001	91%
Surgery time (min)	40±12.1	63±10.6	<0.001	99%

DISCUSSION

Surgical treatment is the preferred treatment for Gartland extension type III supracondylar fractures, in order to provide normal function and to prevent deformity (1-3). CRPP is the gold standard of surgical treatment. In cases where closed surgery is not enough to achieve adequate anatomical reduction and stable fixation, switching to open surgery should be considered (6). All the 50 patients included in the study had Gartland extension type III supracondylar humeral fractures and were treated and followed up by the same surgical team.

In literature, the rate of open presentation of humeral distal pole fractures varies between 5% and 10% (2). All patients in our series presented to the emergency department with closed fractures.

Supracondylar humeral fractures are often seen in children under 10 years of age. The mean age of the patients in our study was 6.6 years (range=1-13 years). Males (58%) and left upper extremity (68%) were dominant in accordance with literature (2).

When supracondylar humeral fractures are treated with CRPP, hospitalization periods are shorter than with open surgery, and there is a decrease in the incidence of complications such as infection and joint stiffness. However, in patients with no satisfactory results after closed reduction due to high fracture displacement, swelling, edema, and soft tissue damage, open precedures should be considered (7-9). In our study, patients who were operated upon late or underwent open surgery had a longer hospital stay than other patients. Although there

are publications reporting 73% of open surgery rate, this rate is between 10% to 15% on average, in literature (9-12). In our series, open reduction was performed in 15 cases (30%), higher than that in literature. Despite the absence of significant data, we thought that this high rate was due to delayed transfer of patients from the primary and secondary health care facilities to the upper center where definitive treatment was done. This delay causes an increase in soft tissue swelling and edema, which prevents effective closed surgery.

Early surgical treatment affects both cosmetic and functional results and reduces complication rates (13). There was no significant difference between the groups in terms of cosmetic and functional results. However, when the patients were divided into groups in terms of surgical method, functional results of the patients treated with open surgery were significantly worse than closed surgical group.

Supracondylar humeral fractures are one of the orthopedic emergencies (2). Prolonged preoperative waiting times are effective in increasing the regional soft tissue swelling and thus, reduce the chance of closed reduction. There is no consensus in literature on the effect of prolonged waiting time on complications and outcomes. In some studies, the results obtained from open or closed surgical treatment within 12 hours are not different from the ones operated after 12 hours (14,15). Conversely, there are publications that suggest that early surgery facilitates surgical fracture reduction (16). In our study, no difference was found between the patients who underwent surgery in the early and the late groups, in terms of cosmetic and functional results.

According to Flynn criteria, Fowles and Kassab (17) reported 87.5%, Davis et al. (18) 80% and Sharma et al. (19) achieved 90% satisfactory results. We found a rate of 94%, which is consistent with that found in literature.

One of the most common early complications of open or closed surgical treatment of supracondylar humeral fracture is pin tract infection. In literature, the frequency of pin tract infection varies and is found between 2.5% and 35.6% (20,21). Acute nerve injury data have also been reported between 10% and 20% (18). No acute nerve injury was observed in our study, and only 1 patient (2%) developed superficial pin tract infection, treated with oral antibiotherapy.

CONCLUSION

In conclusion, unstable supracondylar humeral fractures are common in childhood, and require urgent surgical intervention. The main purpose is to provide early anatomic reduction and stabilization and achieve satisfactory functional and cosmetic results subsequently.

There was no significant difference observed in terms of waiting time for surgery and cosmetic and functional outcomes of patients. However, we observed that early surgical treatment reduces operative time, C-arm fluoroscopy usage, hospital stay, and open surgery ratio. We propose that Gartland type III supracondylar humeral fractures should be treated with closed surgical method within the first 12 hours considering the negative effect of open reduction on functional outcomes.

Ethics

Ethics Committee Approval: Okmeydanı Training and Research Hospital 06.02.2018-827.

Informed Consent: Informed consent was obtained from all individual participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.D.B., M.Y., S.S.D., Y.İ., M.Ç.K., A.Ç.T., Concept: C.D.B., M.Y., S.S.D., Y.İ., M.Ç.K., A.Ç.T., Design: C.D.B., M.Y., S.S.D., Y.İ., M.Ç.K., A.Ç.T., Data Collection or Processing: C.D.B., M.Y., S.S.D., Y.İ., M.Ç.K., A.Ç.T., Analysis or Interpretation: C.D.B., M.Y., S.S.D., Y.İ., M.Ç.K., A.Ç.T., Literature Search: C.D.B., M.Y., S.S.D., Y.İ., M.Ç.K., A.Ç.T., Writing: C.D.B., M.Y., S.S.D., Y.İ., M.Ç.K., A.Ç.T.

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Added Value of SPECT/CT to Whole Body Scan Test Planar Imaging in Patients with Thyroid Cancer After Radioiodine 131 Therapy

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Abstract

Objective: The aim of this retrospective study was to determine added value of single photon emission computed tomography (SPECT)/computed tomography (CT) imaging to whole body scan (WBS) planar imaging in patients with thyroid cancer after radioiodine 131 ablation therapy.

Methods: Indications for treatment of radioactive ablation therapy were postsurgical ablation, recurrent or metastatic disease with high thyroglobulin level of 50 patients with thyroid cancer were evaluated. Following 6 or 7 days after the between 50 and 300 mCi of radioiodine 131 administered orally in patients examined with WBS planar imaging, suspicion of metastasis evaluated with SPECT/CT imaging method. Imaging techniques were evaluated by nuclear medicine specialist with over 10 years experience in thyroid cancer management. The number of lesions assessed with planar images and the number of lesions assessed with SPECT/CT were recorded. The difference between the level of significance was tested using Wilcoxon Signed Rank test, SPSS 12 software package. Special cases with lesion based analysis was performed by examining the reviews.

Results: On planar images 188 foci were detected, on SPECT/CT images 196 foci were detected. Difference between the number of detected lesions was found to be a statistically significant ($p<0.05$). SPECT/CT added diagnostic value 117 of 188 foci over planar imaging.

Conclusion: In patients with thyroid carcinoma, there was a statistically significant difference between the number of lesions detected with WBS planar imaging and the number of lesions detected with SPECT/CT.

Keywords: Radionuclide imaging, SPECT and CT, thyroid carcinoma

INTRODUCTION

The incidence of differentiated thyroid cancer (DTC) in the last three decades has increased in men and women (1,2). Some studies have suggested that the use of ultrasonography and verification methods with fine needle aspiration biopsy explain this increase (3,4). DTC is the most common type of cancer among endocrine system malignancies. Thyroid cancers occur at an earlier age than many adult cancer types, the median age at the time of diagnosis is 54 in men and 48 in women. The treatment method chosen in 84% of patients is total thyroidectomy, and 15% is partial thyroidectomy. Approximately 56% of the good DTCs treated surgically receive radioactive iodine (RAI) 131 therapy for ablation of the remaining residual tissue. By suppressing the pituitary gland, suppression therapy with levothyroxine is applied to prevent the secretion of thyroid-stimulating hormone (thyrotropin). In this way, recurrence rates

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are tried to be reduced. The relative 5-year survival rate for all thyroid cancer patients is 97.3%. The stage of the disease and the age of the patient at the time of diagnosis affect the survival time. The 5-year survival rate is 99.8% in localized disease, 96.8% in regional spread, 55.4% in those with distant metastasis (5).

I-131 applied on the 6th or 7th day following the application of RAI ablation therapy in the DTC is included in the routine algorithm of the whole body scan (WBS) (6). Routine imaging is done as planar imaging with gamma camera. Residual tissue, lymphatic or other possible metastases can be imaged during post-treatment imaging. When imaging is done planar, there are deficiencies in terms of anatomical correlation. Due anatomical correlation and three-dimensional imaging can be done by single photon emission computed tomography (SPECT)/CT, additional lesions can be detected which may result in changes in the patient's treatment and follow-up.

The aim of this study is to show whether the contribution of SPECT/CT imaging method on planar imaging after RAI therapy in DTC patients is statistically significant and to examine possible contributions.

METHODS

This study was carried out with the approval decision of Okmeydanı Training and Research Hospital Clinical Research Ethics Committee dated 17.12.2012 and numbered 41. Consent was obtained from the patients who were scanned.

Cases

The patients who received 50-300 mCi RAI treatment in our clinic between April 2010 and October 2011 due to thyroid cancer and who underwent planar scintigraphy imaging 4 or 7 days after treatment, and from the activity involvements with suspicion of metastasis or recurrence and/or those investigated with SPECT/CT with need of an anatomical correlation were chosen. No exclusion criteria were applied. It was observed that the patients whose dossier and epicrisis information were examined were followed up and received RAI treatments in accordance with the patient preparation protocol before RAI treatment.

Imaging Technique

1- Patient Preparation: The patients are informed about the method of scan, and the importance of their immobility throughout the study is explained.

2- Imaging: Imaging of all cases was done with Infinia double headed gamma camera or Infinia Hawkeye 4 (General Electric Medical Systems, Milwaukee, WI) double headed gamma camera. After WBS was performed, SPECT/CT examination was performed for those with suspected recurrence and metastasis, and the relevant field of view; viewing area was determined by the nuclear medicine specialist who evaluated the WBS image.

a. Planar imaging: WBS planar imaging was taken at a speed of 10 cm/minute, and spot images were taken in 5 minutes with Infinia double-head gamma camera or Infinia Hawkeye 4 (General Electric Medical Systems, Milwaukee, WI) double-head gamma camera.

b. SPECT/CT imaging: SPECT imaging was done with Infinia-Hawkeye 4 (General Electric Medical Systems, Milwaukee, WI) device after planar imaging evaluation. With wide field of view, high energy, high resolution, parallel hole collimator, 60 images were taken in total 360 degrees with zoom value at 1, peak energy level 364 KeV, window range 10%, each image 30 seconds, 128x128 matrix, 6 degrees step and shoot mode. CT imaging was performed with Infinia-Hawkeye 4 (General Electric Medical Systems, Milwaukee, WI) device without giving oral or intravenous contrast agent immediately after SPECT imaging. In the system containing low dose CT (4 slice), the settings of the X-ray tube were determined at 140 kV and 2.5 mA, in the mode of scan type being helical, with a wide viewing angle in the pitch of 1.9, 512x512 matrix in half rotation. Standard filter is applied to the images obtained. The scan time lasted about 4.5 minutes for 40 cm in helical shooting.

Evaluation Criteria

Planar and SPECT/CT images were evaluated by a nuclear medicine specialist with more than 10 years of experience in thyroid cancer imaging. Apart from nuclear medicine scintigraphic images, clinical information, laboratory values and available radiological images were also taken into consideration during the evaluation.

During the evaluation of scintigraphic findings, one or more activity areas with more involvement than background activity were positively evaluated. Nasal activity was considered normal. Symmetrical salivary gland activity, gastrointestinal activities, bladder activity were evaluated as normal. Diffuse activity involvement in the liver was considered normal in people with functional thyroid tissue. The activity involvement areas in other areas were recorded as abnormal.

SPECT images were performed on Xeleris (General Electric Medical Systems, Milwaukee, WI) workstation. Qrecon Quant filter was used as reconstruction downhill filter. After filtering with the Hann prereconstruction filter (frequency value 0.9), it

is reconstructed with OSEM iterative image refresh technique, while the subset value was 10 and refresh value was 2. Filtered with Hann 3D post reconstruction filter (frequency value 0.9). Fusion images were obtained by combining the SPECT images with attenuation correction by computer and CT images. It was evaluated whether SPECT/CT images are synchronized with regions with RAI involvement in transverse, coronal, sagittal sections and 3D images.

Lesion numbers were recorded in both imaging methods for statistical analysis. For each lesion, it was classified as malignant or benign by making anatomical correlation with SPECT/CT and the contribution rate of SPECT/CT was recorded in the lesion-based analysis.

Statistical Analysis

SPSS 12.0 software package was used for statistical analysis. In order to determine the appropriate test to be used in the evaluation of the difference in the number of lesions between planar imaging and SPECT/CT imaging, it was first examined whether the variables were normally distributed or not. The Wilcoxon Signed Rank test was used to analyze the difference in the number of lesions, since the normal distribution assumption did not occur. Hypotheses for testing were established as follows.

H_0: There is no statistical difference between the number of lesions determined by planar imaging and the number of lesions determined by SPECT/CT imaging.

H_1: There is a statistical difference between the number of lesions determined by planar imaging and the number of lesions determined by SPECT/CT imaging.

95% significance level ($p<0.05$) was used in the tests.

Lesion-based analysis was performed. Differences between the planar imaging method and SPECT/CT were recorded. The contribution value of SPECT/CT was calculated as a percentage.

RESULTS

The cases were between the ages of 18-80. The average age was calculated as 47.60±16.05 (Table 1). Of the 50 patients, 42 (84%) were female and 8 (16%) were male (Figure 1).

A total of 188 lesions were detected on planar images and 196 lesions on SPECT/CT images (Table 2).

Table 1. Distribution of cases by age

	n	Minimum	Maximum	Average	Standard deviation
Age	50	18	80	47.60	16,05475

The dose of RAI applied to the cases is in the range of 50-300 mCi. The average RAI dose was calculated as 131.40 mCi.

There was a statistically significant difference in terms of the number of lesions determined by planar imaging and SPECT/CT imaging ($p>0.05$). The test results are shown below (Table 3).

Lesion-based analysis; contribution after evaluation of lesions considered suspicious in planar imaging with SPECT/CT; a total of 188 lesions were detected in planar imaging, and 196 lesions in SPECT/CT imaging. When 117 lesions considered suspicious in planar imaging were evaluated by SPECT/CT, 44 were defined as benign and 73 as malignant lesions.

Anatomic correlation was performed for all other lesions in the SPECT/CT imaging area (Table 4).

DISCUSSION

Unlike other imaging modalities, there are unique methods of defining physiological activities and processes using nuclear medicine techniques. Most of the time, knowing the physiological activity involvement helps in the interpretation of the examination. When an unusual involvement is detected in imaging, it is important to determine the exact localization of the lesion for the planning of treatment. Determination of the exact localization has become possible today with the SPECT/CT imaging method (7). By combining anatomical and molecular imaging methods with devices such as SPECT/CT and PET/CT, more precise comments can be made regarding better attenuation correction, better anatomic correlation and examinations (7).

In thyroid cancer patients, WBS performed on the 5th-8th days after RAI ablation therapy is used as a standard imaging method. Important information about the condition of the disease is

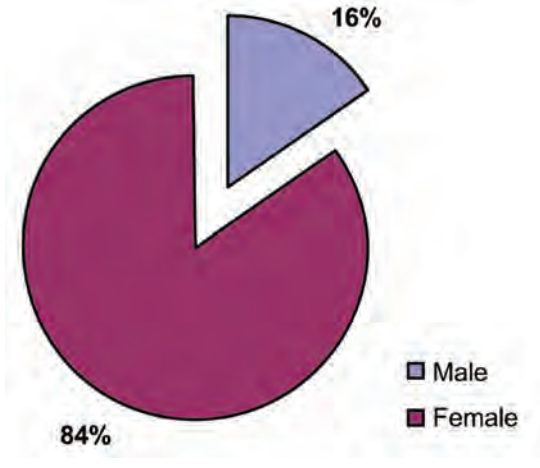

Figure 1. Distribution of cases by gender

Table 2. Planar and SPECT/CT imaging lesion count and pathological diagnosis of cases			
Case Id	**Planar imaging lesion count**	**SPECT/CT lesion count**	**Pathological diagnosis**
1	1	1	Papillary carcinoma follicular variant
2	4	4	Multicentric papillary carcinoma
3	4	4	Papillary carcinoma classic
4	2	2	Papillary carcinoma classic
5	10	11	Papillary carcinoma classic
6	4	5	Follicular carcinoma
7	5	5	Papillary carcinoma classic
8	4	4	Papillary carcinoma classic
9	1	2	Papillary carcinoma classic
10	5	5	Papillary carcinoma classic
11	4	4	Papillary carcinoma classic
12	4	4	Papillary carcinoma classic
13	3	3	Papillary carcinoma follicular variant + opposite lobe papillary microcarcinoma
14	5	5	Follicular carcinoma
15	3	5	Papillary carcinoma classic
16	3	3	Papillary carcinoma classic
17	3	3	Papillary carcinoma classic
18	2	2	Papillary carcinoma classic
19	9	9	Met: follicular carcinoma + slightly differentiated carcinoma
20	5	6	Papillary carcinoma classic
21	9	9	Papillary carcinoma classic
22	2	2	Papillary carcinoma follicular variant + opposite lobe multicentric papillary microcarcinoma
23	3	3	Diffuse invasive follicular carcinoma + papillary carcinoma follicular variant
24	4	4	Papillary carcinoma classic
25	1	1	Papillary carcinoma classic
26	4	4	Papillary carcinoma classic
27	4	4	Papillary carcinoma classic
28	5	5	Papillary carcinoma classic
29	2	2	Multicentric papillary microcarcinoma
30	3	3	Papillary carcinoma classic
31	5	5	Papillary carcinoma classic
32	2	2	Multicentric papillary carcinoma
33	2	1	Papillary carcinoma classic
34	3	3	Papillary carcinoma classic
35	3	3	Multicentric papillary microcarcinoma
36	2	2	Papillary carcinoma classic
37	7	8	Metastatic thyroid carcinoma
38	3	3	Papillary carcinoma classic
39	1	1	Papillary carcinoma slightly differentiated insular
40	4	4	Papillary carcinoma classic
41	3	3	Papillary carcinoma classic
42	4	4	Papillary microcarcinoma classic type + follicular variant
43	4	4	Papillary microcarcinoma

Table 2. Continued			
Case Id	**Planar imaging lesion count**	**SPECT/CT lesion count**	**Pathological diagnosis**
44	2	2	Minimally invasive follicular carcinoma
45	3	3	Papillary carcinoma classic
46	5	5	Mixed type of papillary carcinoma
47	9	11	Papillary carcinoma classic
48	2	2	Papillary carcinoma classic
49	3	3	Papillary carcinoma classic
50	3	3	Papillary carcinoma follicular variant
Total	188	196	
SPECT: Single-photon emission computed tomography, CT: Computed tomography			

Table 3. Wilcoxon signed ranks test results				
Ranks				
		n	**Mean Rank**	**Sum of Ranks**
SPECT-CT - planar	Negative ranks	1 (a)	3.50	3.50
	Positive ranks	7 (b)	4.64	32.50
	Ties	42 (c)		
	Total	50		
Test statistics				
	SPECT-CT - planar			
Z	-2.126 (a)			
Asymp. Sig. (2-tailed)	0.033			
a SPECT-CT < planar, b SPECT-CT > planar, c SPECT-CT=planar a: Based on negative ranks, b: Wilcoxon signed ranks test				

Table 4. Lesion-based analysis			
	Lesion count	**Impact of SPECT/CT**	**Contribution percentage**
Total lesion - planar/ SPECT-CT	188/196	Increase in lesion detection	4.3%
Diagnostic contribution of SPECT/CT	117/188	Increased determination in localization and characterization (benign/ malignant)	62.2%
Anatomical correlation	71/188	Increase in localization determination	27.8%
SPECT: Single-photon emission computed tomography, CT: Computed tomography			

obtained after treatment with WBS. Although RAI involvement is specific for thyroid tissue, many false positive conditions such as contaminations, physiological excretions can occur in planar scintigraphy, and a definite anatomical correlation is needed to distinguish between a physiological condition and a malignant lesion. By determining the exact anatomical localization of RAI involvement with SPECT/CT, diagnostic accuracy is increased and a positive contribution is made to the management of patients' treatment (8-10). Before the clinical use of the SPECT/CT device became widespread, it was attempted to examine SPECT and CT by using computer fusions after performing on separate devices, and to use external markers outside the body, and publications have been published on the usefulness of these (11,12).

In this study, the cases with suspicious involvements during WBS planar imaging performed after RAI ablation therapy in thyroid cancer patients were evaluated for those who were identified and/or anatomically correlated with SPECT/CT. It is aimed to examine the contributions of SPECT/CT to planar imaging. For this purpose, whether there is a statistical difference between the number of lesions detected in planar imaging and the number of lesions detected in SPECT/CT was tested with the SPSS 12.0 package program Wilcoxon Signed Rank test and the result was found to be statistically significant. The total number of lesions detected in planar imaging was 188, the number of lesions detected in SPECT/CT was 196, and the rate of increase was calculated as 4.3%. In addition, the contribution of SPECT/CT was evaluated by performing lesion-based analysis. According to the result of the lesion-based analysis; it was found that SPECT/CT was useful in defining RAI involvement in 117 (62.2%) of 188 lesions detected in planar imaging. It has been observed that it also contributed to the anatomical correlation of all remaining foci of involvement (27.8%).

In a study conducted by Ruf et al. (13), which included 24 thyroid cancer patients who could not be concluded with full-body-scan planar imaging after RAI ablation therapy (3.7 GBq=100 mCi); by comparing SPECT and SPECT/CT imaging methods, it was examined whether fusion imaging contributed. As a result of the study, in focus-based examination; SPECT/CT provided important clinical information by providing comment changes in 15 (38%)

out of 39 focal points. In patient-based examination; these findings were found to be significant in 6 (25%) of 24 patients, and SPECT/CT fusion was suggested to rule out artifacts. Compared to this study, it is seen that similar results are obtained. It was thought that the variance in contribution percentage of SPECT/CT may be related to the selection of patients.

In the study conducted by Schmidt et al. (14) to evaluate the contribution of SPECT/CT to nodal staging in 57 thyroid cancer patients after RAI ablation therapy; the cervical region was evaluated with planar imaging and SPECT/CT. SPECT/CT led to a revision in the original diagnosis of 28 of the 143 RAI involvement foci detected in planar imaging. In particular, it classified 6 of the 11 focal points considered as lymph node metastasis in planar imaging and 11 of the 15 unidentified focuses as benign, and identified 11 focal points as lymph node metastasis which were previously defined as thyroid balance or ambiguous in planar imaging. SPECT/CT contributed to nodal staging in 20 (35%) of 57 patients, and changed the nodal staging from N0 to N1 in 2 of 20 patients and from N ambiguous (Nx) to N1 in 6 of 30 patients. According to these results, it changed the risk layer in 14 of 57 patients according to International Union Against Cancer. Although nodal staging was not taken into consideration in this study, a full comparison could not be made, but 117 of 188 focal points detected in planar imaging were identified as suspicious, and 44 of these foci were classified as benign and 73 were malignant with SPECT/CT, which suggests that these two methods provide information in the same direction.

In the study conducted by Aide et al. (15), 55 thyroid cancer patients undergoing RAI treatment were evaluated and it was shown that cases identified as ambiguous by planar imaging decreased from 29% to 7% with SPECT/CT. In addition, compared to planar scintigraphy, SPECT/CT has been shown to be superior in predicting treatment failure. In this study, there was no lesion that SPECT/CT could not identify among the involvement detected uncertain in planar imaging.

In a dicentric study of Mustafa et al. (16), 151 cases of T1 stage papillary carcinoma, 96 of which were papillary microcarcinoma were evaluated; cervical lymph node dissection was performed in 69 patients and SPECT/CT based nodal staging was performed in the remaining 82 patients. The incidence of lymph node metastasis was 26% in the whole group and 22% in the papillary microcarcinoma group. It was determined that SPECT/CT provides more accurate information in 24.5% of patients compared to planar scintigraphy. In this study, no comment was made on the diagnostic accuracy of SPECT/CT in nodal staging due to the absence of histopathological verification.

In the study conducted by Ciappuccini et al. (17) on 170 DTC patients; after RAI ablation therapy, the effects of other prognostic factors such as age, gender, stimulated triglyceride (Tg) level, tumor, lymph node metastasis, macroscopic lymph node involvement on disease-free survival with the neck and thorax SPECT/CT examination were compared. WBS showing positive RAI involvement only and A Tg negative, Tg level at least 58 ng/dL were found to be associated with an increased risk of recurrence or persistent disease.

Chen et al. (18) performed 37 SPECT/CT studies where 23 patients with locally advanced or metastatic thyroid carcinoma failed to achieve any results with planar imaging after RAI ablation therapy; they found that it contributed to the diagnosis in 17 of 23 patients (74%). They reported that treatment strategy changed in 8 (35%) of 23 patients with SPECT/CT imaging. They reported that the diagnostic accuracy of fusion SPECT/CT imaging was greater than planar scintigraphy, reduced trap images, and caused a change in treatment strategy.

It was observed that the findings detected in many studies and the findings found in this study were compatible and supportive. In this study, it was seen that SPECT/CT is a contributing imaging method for characterizing suspicious involvements in planar imaging and making anatomical correlations.

In the clinic where the study was performed, the indication for performing SPECT/CT examination in patients included in the study was suspicious involvement in WBS and the need for anatomical correlation (Figure 2-4). After RAI ablation therapy of thyroid cancer patients, WBS testing continues to be performed with planar imaging as a routine application in the patient group. In other words, SPECT/CT imaging is not routinely applied to all patients. The reason why it is not routinely applied in all patient groups; although the CT component of the SPECT/CT device produces lower dose radioactivity than conventional CT imaging devices, it is to keep the radiation dosimetry low. It was mentioned earlier in this section that there were publications that showed that SPECT/CT detected lesions that could not be detected in the planar image and lesions in even WBS negative cases. In the clinic where this study was performed, WBS negative patients could not be included in the study because SPECT/CT was not performed. It may be thought that the patient group of the cases with suspicious findings in WBS, which caused the narrowing of the patient group in the study. It was thought that studies should be conducted in multi-centered, wider patient groups in order to comment on whether SPECT/CT should be applied to all cases as a routine practice.

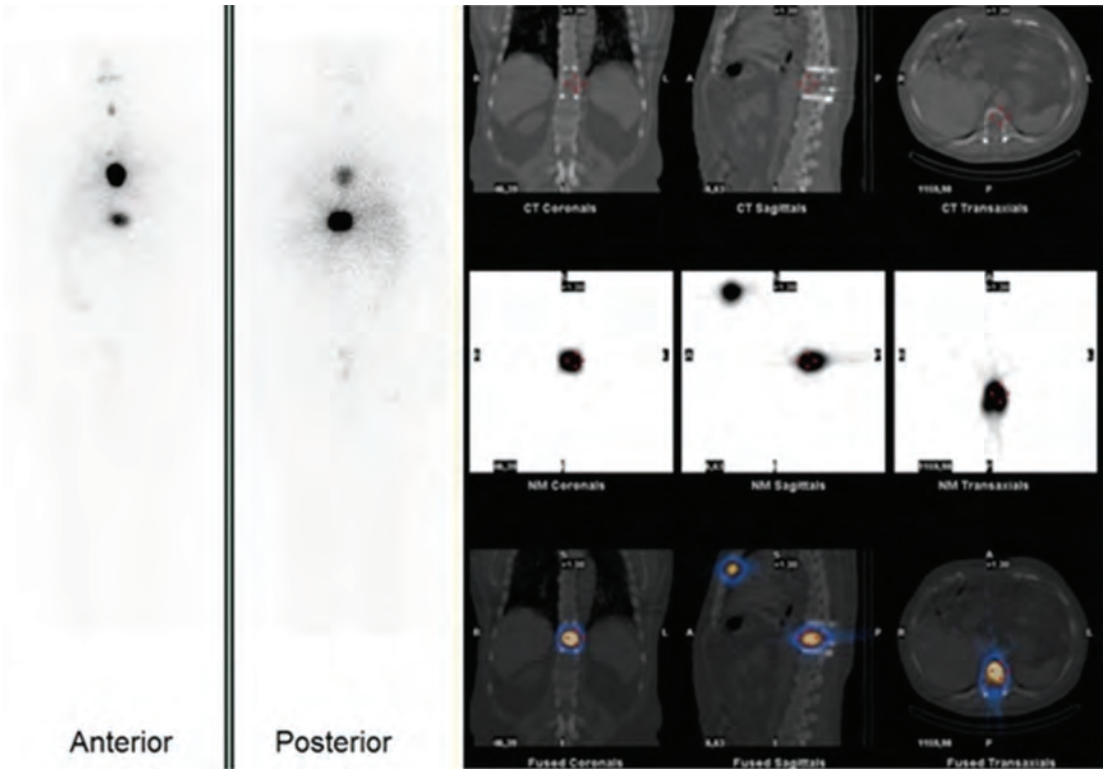

Figure 2. A 56-year-old male who had papillary carcinoma metastasis as a result of the pathology of the mass excision from the dorsal vertebra 16 months ago, underwent bilateral total thyroidectomy 14 months ago. The patient, whose pathology result was reported as follicular variant of papillary carcinoma, was administered 150 mCi RAI treatment. Local recurrence and lung metastasis were detected in I-131 WBS during follow-up. In the WBS performed on the 7th day of the patient who received 200 mCi RAI treatment, mild RAI involvement in the thyroid lodge, severe RAI involvement in the midline in the mediastinum and mild RAI involvement in the right of the midline and more severe RAI involvement in the posterior position were observed in the dorsal area. In the planar image with SPECT/CT, it was observed that RAI involvement observed in the middle part of the mediastinum was in the sternum, and the involvement in the dorsal area was in the D10-11 vertebrae. In the CT component of SPECT/CT, the appearance of the screws placed in the operation through the dorsal vertebra is observed. With SPECT/CT, the location of RAI involvement was precisely determined and anatomical correlation was made. Lesions were reported as metastasis
RAI: Radioactive iodine, WBS: Whole body scan, SPECT: Single-photon emission computed tomography CT: Computed tomography

In this study, 188 RAI involvement focuses were detected in WBS planar imaging, and 196 RAI involvement focuses were detected with SPECT/CT, and it was found that there was a statistically significant difference. SPECT/CT provided additional clinical information or helped lesion characterization in 117 of 188 RAI involvements observed on WBS planar imaging. The contribution of found foci on staging has not been studied separately, the first reason for this was there were patients who were at a high stage in the patient group and who underwent RAI due to high Tg at follow-up, and second reason was the idea that it would be more meaningful to do it in a larger patient series. It has been observed that the CT component of SPECT/CT contributes by changing the treatment course in some cases. For example, in one case, the pulmonary consolidation area was monitored, and the focus detected in favor of metastasis in the consolidation area, and it was seen that it could make changes in the course of treatment.

CONCLUSION

It is thought that conducting such researches, which will enable the role of SPECT/CT to be better determined in the process of thyroid cancer follow-up, may contribute to better follow-up of doctors. According to this study, SPECT/CT is a recommended imaging method for lesions in which planar imaging is suspected or requires anatomical correlation after RAI ablation therapy of thyroid cancer.

Acknowledgement

This article was compiled from the medical speciality thesis titled "Added value of SPECT/CT to whole body scan test planar imaging in patient with thyroid cancer after radioiodine 131 therapy", presented by Mehmet Tarık Tatoğlu at Nuclear Medicine Clinic of Okmeydanı Training and Research Hospital.

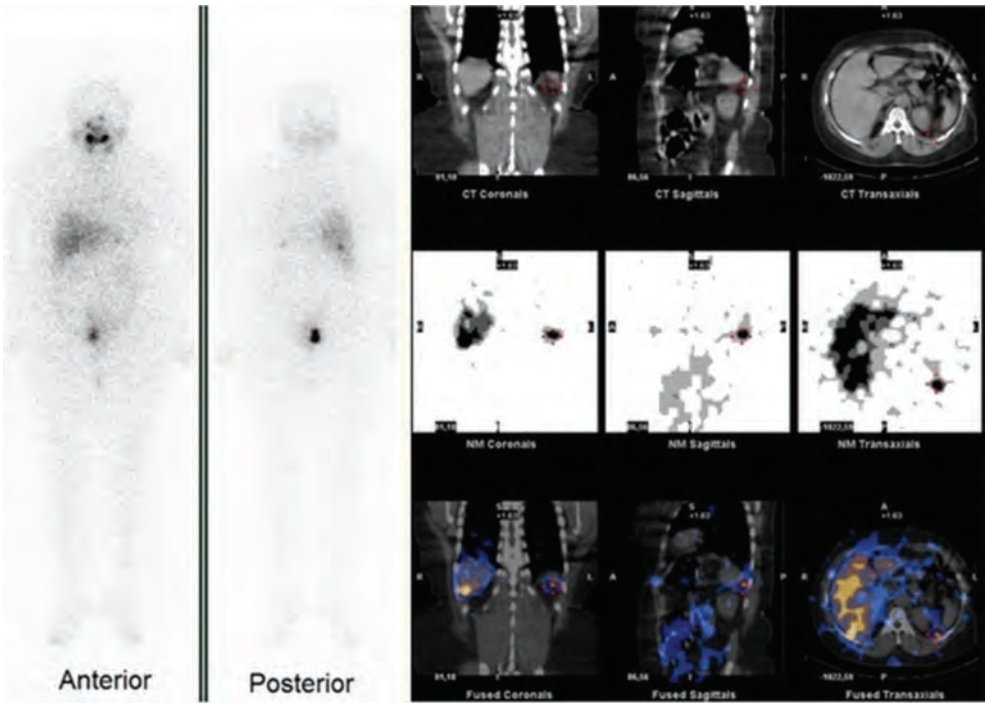

Figure 3. A 55-year-old female who underwent bilateral total thyroidectomy and received 100 mCi RAI ablation therapy due to the pathology result of multicentric papillary carcinoma, SPECT/CT imaging was performed due to the detection of suspicious foci on the right and left sides of the abdomen in the WBS on the 7th day of the treatment. In SPECT/CT images, one intense RAI involvement was observed in the 6th segment of the liver and adjacent to the ribs in the inferoposterior of the spleen. In planar imaging with SPECT/CT, the RAI involvements observed as suspicious in the abdomen were anatomically correlated and metastasis was reported

RAI: Radioactive iodine, WBS: Whole body scan, SPECT: Single-photon emission computed tomography CT: Computed tomography

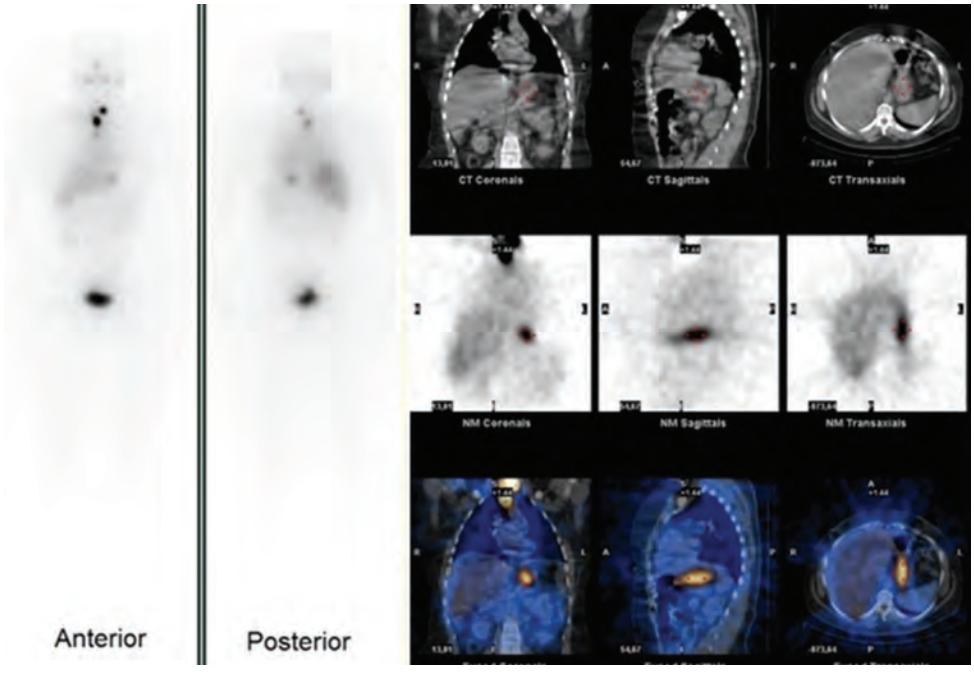

Figure 4. RAI treatment due to the pathology result of papillary carcinoma with capsular invasion and vascular invasion, SPECT/CT imaging was performed due to suspicious RAI involvement in the upper mediastinum compatible with the residual tissue in the thyroid lodge and in the left midline in the abdomen in the WBS performed on the 7th day of the treatment. SPECT/CT images showed an involvement consistent with metastatic LAP in the upper mediastinum, while benign activity involvement consistent with the stomach was observed in the left midline of the abdomen. With SPECT/CT, in this case one suspect involvement was reported as malignant and one suspicious involvement was reported as benign

RAI: Radioactive iodine, WBS: Whole body scan, SPECT: Single photon emission computed tomography CT: Computed tomography, LAP: Lymphadenopathy

Ethics

Ethics Committee Approval: Okmeydanı Training and Research Hospital Clinical Research Ethics Committee dated 17.12.2012 and numbered 41.

Informed Consent: Form was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T.T., T.Ö., F.Ö., M.M., Concept: M.T.T., T.Ö., M.M., Design: M.T.T., T.Ö., M.M., Data Collection or Processing: M.T.T., H.Ö., Analysis or Interpretation: M.T.T., T.Ö., F.Ö., M.M., H.Ö., T.K.G., Literature Search: M.T.T., Writing: M.T.T.

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

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ORIGINAL ARTICLE

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OPEN ACCESS

Risk Factors and Response to Treatment of Chronic Migraine Patient

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Abstract

Objective: Migraine is a common cause of medical consultation in neurology policlinics. Chronic migraine usually develops as a complication of episodic migraine. It causes significant distress with substantial impact on the quality of life of an individual and huge economic cost to the society through occupational disability and healthcare consultations. Chronic migraine and medication-overuse headache often coexist. The aim of this study was to determine the risk factors for the transformation to chronic migraine and treatment for chronic migraine.

Methods: One hundred thirty-nine patients diagnosed with chronic migraine between January 2014-January 2015 were included in the study. These patients were observed for risk factors and prophylactic treatment.

Results: 92.8% of the patients in the study were female and were between the ages of 18-63. 85% of patients had headache for more than five years. Risk factors for the transformation from episodic to chronic migraine were determined as low-level of education, low-middle social economic status, emotional stress, obesity and sleep disorders. All patients were treated with prophylactic treatment. 19 patients were not evaluated because they failed to follow the protocol of treatment. 72% of patients responded to treatment and 27.5% of patients failed treatment. It was determined that only the accompanying depression had a negative effect on treatment response.

Conclusion: In our study, female gender, low educational level, low-middle socioeconomic level, obesity, preobesity, comorbid psychiatric disease and analgesic overuse have been shown as risk factors for the transformation from episodic to chronic migraine. Prophylactic drugs used in the treatment of episodic migraine had similar rates of response to treatment when used in chronic migraine prophylaxis. Treatment with botulinum toxin A and dry needle therapy used in the treatment-resistant patient has been shown to significantly increase treatment compliance and response. The presence of depression has been shown to negatively affect treatment.

Keywords: Chronic migraine, risk factors, treatment

INTRODUCTION

Migraine is a multifactorial neurovascular syndrome characterized by episodes of headache that occur with various triggering factors in people with genetic sensitivity. For three months and more, headache for 15 days a month, at least 8 of which are of migraine character, is chronic migraine (1). The prevalence of migraine is about 15-20% (2,3). Migraine is chronic at a rate of 4% per year (4). The prevalence of chronic migraine in society is about 2% (5). Chronic migraine causes serious deterioration in the quality of life and economic loss of patients (6,7). Patients develop a high rate of relapse after treatment, which is a problem in treatment and follow-up (8). Various risk factors facilitate the transformation of episodic migraine (9-13). In this study, we aimed to determine the risk factors that facilitate chronic pain in patients diagnosed with chronic migraine and to analyze treatment responses.

METHODS

In January 2014-January 2015, patients aged 18-65 who were diagnosed with chronic migraine were included in this study

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retrospectively in the neurology clinic headache outpatient clinic of the Ministry of Health Okmeydanı Training and Research Hospital. Our study was approved by the Ethics Committee of Saglık Bilimleri University Okmeydanı Training and Research Hospital dated 14.04.2015 and numbered 303. Demographic findings, causes that may be risk factors for chronic pain, accompanying comorbidities, causes that predispose pain, Hamilton depression scales were examined.

Migraine treatments applied to patients were recorded from patient files. The risk factors that may lead to chronic headache were examined. Their responses to different treatments were analyzed and the effect of risk factors on treatment response was evaluated.

Statistical Analysis

Descriptive statistics are presented as mean, standard deviation and percentage. The mean of the quantitative data was compared with the t-test, while the broad properties of the ordinal and variance were compared with the Mann-Whitney U test. The categorical data was evaluated with chi-square or Fisher tests and the significance level of $p<0.05$ was accepted in all tests.

RESULTS

One hundred thirty-nine patients were enrolled in the study. Of the patients, 129 (92.8%) were female and 10 (7.2%) were male. The mean age of the patients was 41.5±10.8. Demographic findings on age, duration of headache, duration of migraine diagnosis, duration of chronic headache and number of days of headache per month are summarized in Table 1.

77.7% (n=108) of the patients were married and 28.7% (n=40) were working in a regular job. 13.7% of patients (n=19) stated that their income was poor, while 77% (n=107) stated that they were normal (based on the minimum wage for 2015). In 88.5% of patients (n=123) headache onset age was under 40 years of age, total headache duration ranged between 8-480 months, mean 169.2 months, migraine diagnosis period ranged between 0-480 months, mean 80.8 months and average number of head pain days per month was 23.9±5.7 days/month. The visual analog scale score of 83.4% (n=116) of the patients was 8 and above. 61.9% (n=86) of the patients had primary school and below education level. 41.7% (n=58) were preobes [body mass index (BMI): 24-30 kg/m^2], 28.8% (n=40) were obese (BMI: 30-40 kg/m^2) and 2.9% (n=4) were morbidly obese. 31.7% of the patients were over the obesity limit and 73.4% were overweight and above. The average number of applications to the emergency department in the last year was 7.07 days/year. 81.3% of patients had been admitted to multiple centres for headaches. While 43.9% (n=61) had no comorbidity, 20.1% (n=28) had more than one comorbidity. The accompanying comorbidities are indicated in Table 2.

71.2% of patients (n=99) had overuse of analgesics. Overused analgesics were 41.7% (n=58) non-steroidal anti-inflammatory (NSAIDs), 10.8% (n=15) ergotamine, 1.4% (n=2) triptan and 17.3% different combinations of these drugs according to their frequency. Prophylactic treatment was initiated for all patients enrolled in the study. Because 19 patients did not continue follow-up, the treatment response could not be assessed. 50% and above decrease in pain frequency after taking prophylactic treatment at appropriate dose for at least 3 months was evaluated as a positive response to the treatment. 72.5% (n=88) of the follow-up patients received response to the treatment. The responses of patients to different treatment protocols are summarized in Table 3.

The effects of demographic findings, risk factors, accompanying comorbid diseases, pain predisposing factors and clinical findings

Table 1. Demographic findings of patients (n=139)

Parameters	Minimum	Maximum	Mean
Age	18	64	41.5±10.8
Headache duration (months)	8	480	169.2±114.6
Diagnosis of migraine (month)	0	480	80.8±92.4
Chronic headache duration (months)	2	420	53.8±66.7
Number of head pain days per month	15	30	23.9±5.7

Table 2. Accompanying comorbidities

Disease	Frequency	Disease	Frequency
Gastrointestinal disease	%13 (n=18)	Liver disease	%3.6 (n=5)
Hypertension	%12.2 (n=17)	Cardiac disease	%3.6 (n=5)
Thyroid disease	%12.2 (n=17)	Nephrolithiasis	%2.9 (n=4)
Asthma	%9.4 (n=13)	Allergy (other)	%2.2 (n=3)
Psychiatric illness	%8.6 (n=12)	Epilepsy	%2.2 (n=3)
Iron deficiency anemia	%6.5 (n=9)	Vitamin B12 deficiency anemia	%1.4 (n=2)
Diabetes mellitus	%3.6 (n=5)		

Table 3. Prophylactic treatment responses			
Treatment	**Response**	**No response**	**Side effect developed**
Propranolol	%42.9 (n=6)	%57.1 (n=8)	-
Flunarizine	%45.9 (n=28)	%34.4 (n=21)	%19.7 (n=12)
Topiramate	%54 (n=34)	%33.3 (n=21)	%12.7 (n=8)
Sodium valproate	%37.5 (n=6)	%50 (n=8)	%12.5 (n=2)
Venlafaxine	%60 (n=21)	%31.4 (n=11)	%8.6 (n=3)
Amitriptyline	%39.1 (n=9)	%39.1 (n=9)	%21.7 (n=5)
SSRI	%23.1 (n=6)	%69.2 (n=18)	%7.7 (n=2)
Pregabalin	%28.6 (n=2)	%28.6 (n=2)	%42.9 (n=3)
Dry needle	%51.9 (n=14)	%48.1 (n=13	-
Botulinum toxin A	%70.1 (n=25)	%21.9 (n=7)	-
Total	%72.5 (n=88)	%27.5 (n=32)	
SSRI: Serotonin reuptake inhibitor			

on treatment responses were examined. After this examination, it was observed that only the presence of psychiatric illness negatively affected the treatment response. In 21.9% (n=7) of the patients who did not receive treatment response, this rate was 5.7% (n=5) while there was a history of psychiatric illness. Statistically, patients with a history of psychiatric illness responded worse to treatment (p=0.015).

DISCUSSION

According to the definition of the International Headache classification-3, chronic migraine is a headache of 15 days per month and above, with at least 8 of which are migratory in character (1) for more than 3 months. It occurs in about 2% of the world's population and more in women. The transformation of episodic migraine to chronic migraine is the transformation of migraine, which usually develops gradually. Episodic migraines develop into chronic migraines at a rate of about 4% per year. The transformation of migraine is not absolute irreversible, remission can be achieved by spontaneous and/or treatment. Chronic migraines lead to more serious losses in quality of life than episodic migraines, and consequent economic losses. Non-modifiable risk factor for the transformation of episodic migraine and chronic migraine are gender, genetic background, history of head and neck injury, low education level, low socioeconomic status, a lot of stress, starting in a young age, initially high headache frequency, presence of concomitant psychiatric illness and allodynia. The modifiable risk factors for the transformation are snoring, excessive caffeine consumption, obesity, sleep disorders and overuse of analgesics (14). Determining the modifiable risk factors that play a role in the transformation of migraine is effective on treatment responses and the course of the disease.

Migraines and chronic migraines are more common in women. Female sex is thought to be a risk factor for migraine, but it is controversial to think of it as a risk factor in terms of chronic headache. Scher et al. (12) in a study comparing chronic daily headache with episodic headache, the proportion of women with chronic migraines was found to be higher than that of women with episodic migraines. In the Castillo study of 1883 chronic migraine patients, the ratio of male/female was 6.5/1 (15), in the Greater Taipei study of 3377 chronic migraine patients, the ratio was 4.5/1 (16), and in the Baltimore study of 13343 chronic migraine patients, the ratio was 2.5/1 (17). In our study, the female/male ratio of 12.9/1 indicated the predominance of female sex in chronic migraine in line with the literature.

Migraine is most commonly seen in the 30-40 age range and its incidence decreases as age progresses. In a study conducted by Scher et al. (12), it was determined that the frequency of chronic headaches decreased in later ages. According to the same study, 29% of patients with episodic head pain were transformed into chronic headache at the first 1 week after the onset of headache, 8% at 1 week 1 month, 35% at 1 month-10 years, and 28% at more than 10 years. In our study, the mean age of the patients was 41.5±10.8 and 88.5% had headache onset under the age of 40. In 13% of patients, headaches were chronic in the first 1 month, in 50% in 1 month 10 years and in 37% in 10 years and above. This difference in chronic periods may be due to sociocultural and anthropological differences belonging to our society.

Although clinical studies show that migraine develops more often in people with high intellectual and educational levels, community-based studies do not confirm this. Some studies suggest that there may be an increase in the prevalence of headaches with low income status. In a Norwegian study, 22718 patients with no initial headache were followed for 11 years, and the prevalence of high frequency headache and chronic headache was higher in patients with low educational and low socioeconomic levels (18). In a study conducted by Scher et al. (12), those with lower level education than high school were found to be 3 times more risky in terms of chronic headache development than those with higher level education and university education. In our study, in line with the literature, 90.6% of the patients had low-to-medium income status and 61.9% had primary and lower education levels.

Although some studies have shown that chronic migraine is not associated with BMI, numerous epidemiological and clinical studies have shown that underweight, preobesity and obesity are

risk factors for chronic migraine. According to the meta-analysis, preobesite and obesity, especially in female sex, were thought to be risk factors for chronic migraine (19,20).

In the review of Bigal et al. (6) the risk of developing chronic daily headache was 5 times higher in patients with BMI over 30. In three broad epidemiological studies, the effect of BMI on migraine progression was evaluated; in the first study, high frequency migraines were developed in 4.4% of normal-weight patients, while in preobesis group, this ratio was found to be 5.8% and 13.6% in obese patients. This study showed that preobesity and obesity lead to increased risk in the transformation of episodic migraine to high-frequency migraine. In the second study, obesity led to a higher risk increase in chronic migraines than in chronic tension-type headaches. In another study, the prevalence of chronic migraine was found to be 0.9% in normal weight and 3.2% in obese people (21). The results of these studies prove the effect of obesity on migraine progression. In a study by Tietjen et al. (22) on 721 migraine patients, headache frequency and headache related disability rates were found to be significantly higher in the group of patients with obesity and depression compared to the group without obesity and depression, and also in the accompanying anxiety disorder, similar results were obtained. According to the results of the depression scale, the presence of depression in all patients was 62.6%, whereas in the group of patients above the obesity limit, this ratio was 72.7%. These results support the tight relationship between depression and obesity.

Chronic migraine affects the functionality of patients severely. In a community-based study conducted by Bigal et al. (6), more than 50% of chronic migraine patients were unable to do houseworks for at least 5 days per month, while in patients with episodic migraines, this rate was found to be 24.3%. 36.9% of chronic migraine patients and 9.5% of episodic migraine patients reported insufficient participation in family activities. The average number of head pain days per month of the patients evaluated in our study was 23.9±5.7 days/month and 4.2% of the patients had been admitted to the emergency department for headache at least 1 time in the last 1 year. Almost half of the patients have a history of applying to the emergency department and the average number of monthly painful days indicate serious disability.

In the study conducted by Bigal et al. (6), 20.2% of patients with chronic migraine were previously diagnosed with chronic migraine and 13.9% were diagnosed with drug overuse headache or rebound headache. 65.5% of the patients evaluated in our study had previously been diagnosed with migraines and there were no patients diagnosed with chronic migraines in our group. These rates indicate the problem with diagnosis of chronic migraine.

Although migraine has been associated with many psychiatric disorders, few studies have proven the effect of psychiatric comorbidity on migraine progression. In the study by Mathew et al. (23), patients were evaluated with the Minnesota Multiphasic Personality Inventory. Episodic migraines were accompanied by 12.2% chronic daily headaches and 70.5% personality disorder. The most common psychiatric disorders associated with chronic daily headaches were hysteria, hypochondriasis and depression. When patients were evaluated with depression scale, depression was found to be 5% in episodic migraine and 46% in chronic headache. The presence of stress detected by behavioral therapists or psychiatrists was 30.4% in episodic migraine and 67.2% in chronic daily headaches. This study shows that psychiatric comorbidity has an effect on the progression of headache. Our study showed the presence of depression with a 62.6% depression scale in line with the literature. 8.6% of the patients had a history of psychiatric illness (depression, anxiety, panic attacks) before, although this rate is significantly lower than the ratio in the literature, this decrease can be explained by the lack of application of the patients to the psychiatrist, as 91.4% of the patients reported the presence of stress at the time of application that would affect their daily life activities.

In a community-based study by Le et al. (24) on 46418 people, 20-30% comorbid disease was observed in migraine patients. Accompanying comorbid diseases include cardiovascular diseases, stroke, musculoskeletal diseases, low back pain, neck pain, history of head and neck trauma, thyroid gland disease, meniere, allergic disease, asthma, epilepsy, kidney stone, osteoarthritis, scoliosis, osteoporosis, fibromyalgia, autoimmune diseases, systemic lupus erythematosus, psoriasis, rheumatoid arthritis and collagen tissue diseases were found in higher rates in patients with migraine than in patients without migraine. There was no significant difference in the incidence of diabetes mellitus, coronary artery disease, juvenile arthritis and ankylosing spodilitis among the group with and without migraine. In our study, 56.1% of patients had at least 1 comorbid disease. The presence of frequent comorbid disease is important for chronic headache and treatment choice. Accompanying comorbid diseases are summarized in Table 2 according to their incidence.

According to the study conducted by Robbins Headache Clinic on 494 migraine diagnosed patients, migraine was predisposed with 62% stress, 43% weather changes, 40% meal skipping, 38%

sunlight, 31% insomnia, 30% dietary factors, 29% perfume, 26% smoking, 24% stress, 24% sleep, 15% exercise and 5% sexual activity (25). In this study, the factors that predispose the headaches of the patients were summarized in Table 4 in order of frequency. The patients evaluated in our study had many predisposing factors in line with the literature, with the exception being predisposition with exercise and sexual activity, which was detected at low rates.

Unnecessary excessive analgesic use has been cited as a poor prognostic factor for migraines. In many community-based studies, it was observed that migraine was the most risky group of patients in terms of drug overuse headache development. In the American Migraine Prevalence and Prevention study, the increased risk of developing chronic migraine was 2 times higher in migraine patients using barbiturates and opiates. In the study, it was found that triptans did not increase risk in terms of episodic migraine transformation, but initially facilitated transformation in headache high frequency migraines, and there was no risk in NSAIDs (26). In the study by Mathew et al. (23); caffeine combined analgesic, narcotic analgesic and ergotamine use was 6% in the group with episodic headache and 52.4% in the group with chronic headache. In the Norwegian Head-HUNT study, 39.3% of patients who used analgesic almost daily developed drug overuse headaches (27). Bigal et al. (6) in a study conducted by, 24.8% of patients with episodic migraines and 31.6% of patients with chronic migraines were using migraine-specific analgesics for attack treatment. The use of one or more non-prescription analgesics was observed in 82.6% of chronic migraine patients and the average monthly analgesic use was determined to be 15.9 days/month. In our study, the use of analgesics in 71.2% of patients meeting the analgesic overuse criteria was determined. It was found that 41.7% of the patients used NSAIDs, 10.8% of ergotamine, 1.4% of triptan and 17.3% of these drugs in different combinations. In accordance with the literature, excessive use of analgesics accompanies chronic migraine at a high rate and most of the analgesics are used without a prescription. This is an indication that high levels of inappropriate analgesic use in chronic migraine patients are one of the common problems. In a study conducted by Bigal et al. (6), 40% of patients with chronic migraines received prophylactic treatment and the proportion of patients receiving regular treatment was 33.3%. In line with the literature, 46% of the patients evaluated in our study did not receive prophylactic treatment, 36% did not respond to the prophylactic treatment they had previously received, and 18% reported that they had partially benefited from the prophylactic treatment they had previously received. Prophylactic treatment was initiated for all patients, 120 patients were evaluated and 72.5% of patients received positive response after one year of follow-up. Information on prophylactic treatment is summarized in Table 3. In classic agents used in migraine prophylaxis, treatment response was similar to that of episodic migraine. There was a significant decrease in headache frequency and severity in 51.9% of patients after dry needle treatment and 70.1% of patients after botulinum toxin a treatment.

Table 4. Predisposing factors and their incidence

Predisposing factor	Frequency	Predisposing factor	Frequency
Environmental factors	%91.4	Hormonal change	%57.6
Stress	%86.3	Dietary factors	%33.1
Sleep disorder	%86.3	Physical activity	%0.7
Skipping meals	%85.6	Sexual activity	%0

CONCLUSION

Chronic migraine seriously worsens the quality of life of the patients due to its high number of painful days and its severity. Chronic migraine is often accompanied by overuse of analgesics, but it is difficult to treat and follow-up in neurology practice and a high rate of recurrence develops after treatment. In our study, female gender, low socioeconomic level, low educational level, analgesic overuse, obesity and associated psychiatric illness were found as risk factors for chronic headache. Risk factors are determinant in terms of the method to be used in treatment and in terms of prognosis. In chronic migraine, similar treatment response was received with agents used in episodic migraine prophylaxis. In treatment of resistant cases, approximately half of the patients were treated with dry needle in addition to prophylactic treatment, and up to 70% responded with Botulinum toxin A administration. This suggests that dry needle administration and Botulinum toxin A treatment, especially in treatment resistant cases, lead to a significant increase in clinical response and may be used as the main treatment option in resistant cases. As a result of rapid detoxification and transition therapy in patients with analgesic overuse, similar treatment responses were received in the group of patients without analgesic overuse. We attribute the significant increase in patients' response rates to treatment after application to increasing patient compliance by regular follow-up, use of appropriate treatment time at appropriate doses and time.

Ethics

Ethics Committee Approval: Ethics Committee of University of Health Sciences Turkey Okmeydanı Education and Research Hospital dated 14.04.2015 and numbered 303.

Informed Consent: Our study was conducted retrospectively and patient consent was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Analysis or Interpretation: B.K., O.A., S.Ü., Literature Search: B.K., O.A., S.Ü., Writing: B.K., O.A., S.Ü.

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

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OPEN ACCESS

The Effect of Postmastectomy Radiotherapy on Patients with Breast Cancer

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Abstract

Objective: Breast cancer is one of the most common types of cancer in women, and the first-line treatment for it is surgery. Depending on the patient's condition, either of the following may be selected: breast-conserving surgery, modified radical mastectomy, radical mastectomy, or simple mastectomy. According to treatment guidelines, chest wall involvement, axillary lymph involvement, and tumors >5 cm should be treated with radiotherapy. Postoperative radiotherapy is required to provide local control and prevent distant metastases. In addition, chemotherapy in early stage breast cancer with axillary involvement increases survival by preventing distant metastases. The contribution of radiotherapy to local and remote control after mastectomy was examined.

Methods and Results: In this retrospective study, 1,073 breast cancer patients who were admitted to our clinic during a period of five years were included and their postoperative radiotherapy treatment results were evaluated.

Conclusion: In patients undergoing radiotherapy, a 6% local recurrence and 88% survival was found in five years. Also, locoregional recurrence was statistically and significantly lower in those undergoing radiotherapy (p=0.0001).

Keywords: Breast cancer, mastectomy, radiotherapy, local control, distant metastasis

INTRODUCTION

Breast cancer is one of the most common types of cancer in women and the most common cause of female death with a worldwide incidence rate of 29%. A study in the United States reported that every year 46,000 out of 183,000 newly diagnosed breast cancer patients die (1). While breast cancer was detected in 17% of cancer patients who visited our outpatient clinic, the proportion of patients who underwent mastectomy was 60%, which decreased over the years.

Generally, women over 50 years of age, having a relative with breast cancer, and those who give birth to their first child after 30 years of age are considered as the high-risk group (2). Breast cancer has also been associated with environmental factors in patients with similar characteristics. It is rarely seen (1%) and has a poor prognosis in men. Tumor is localized in the upper outer quadrant in 38.5%, in the upper inner quadrant in 14.2%, in the central quadrant in 29%, lower outer quadrant in 8.8%, and lower inner quadrant in 5% of the cases. While it is frequently seen in the left breast, only 1-2% of the cases are bilateral (3).

Pathological features are important in determining the treatment and prognosis of the disease. Breast cancers are broadly classified as ductal and lobular. Ductal cancers further include carcinoma in situ, infiltrative ductal cancer, medullary cancer, tubular cancer, mucinous cancer, infiltrative lobular cancer, Paget's disease, and inflammatory breast cancer.

Moreover, for patients with operable breast cancer at early stages, radical mastectomy, modified radical mastectomy (4), simple mastectomy, and breast-conserving surgery may be used.

Radiotherapy applied accurately to the risk groups increases local control and decreases distant metastasis. In patients with

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positive axillary lymph node and skin involvement >5 cm, or positive surgical margin, and the tumor localized in the inner quadrant or areolar region of the breast, radiotherapy should be applied to the region of mammaria interna (5).

Interestingly, a prolonged survival has been reported with chemotherapy, particularly in patients with T1-2 and axillary involvement. While cyclophosphamide (C), methotrexate (M), and fluorouracil (F) are applied in the low-risk groups, C, adriamycin (A), and F are applied in the high-risk ones (6).

Additionally, tamoxifen, which is an antiestrogen, is used as an adjuvant at daily doses of 20 mg in premenopausal and postmenopausal women (7). It also decreases the risk of breast cancer in the contralateral breast.

Although many variables are thought to affect the prognosis of breast cancer, it is based on the time from treatment to recurrence and the total survival time.

Stromal invasion: It is one of the important prognostic factors. While in situ cancers are noninvasive and treated only by mastectomy, the invasive cancers may require chemotherapy, radiotherapy, and antiestrogen therapy after surgery.

Besides, several prognostic facts have been reported to greatly impact the survival and local control, such as the number of lymph nodes involved in the axillary region, their diameter, and extracapsular invasion are used in staging. While the prognosis of patients with <4 axillary involvements is comparable to those without lymph node involvement, it is worse in the presence of >4 involvements. Thymidine-binding index determines the cells in the synthesis (S) phase of the tumor, and is considered as the basis of the decision to administer chemotherapy in patients with risk of early recurrence (8). The tumor-doubling time differs in every tumor. Large tumors generally have higher grades and frequent lymphatic invasion with worse prognosis. While the axillary lymph node involvement in tumors <1 cm in size is seen in 25% of the cases, its incidence rises up to 78% in large tumors (9). Moreover, medullary, tubular, mucinous, and adenoid cystic cancers have a relatively good prognosis, however, the signet ring cell, inflammatory types, and carcinosarcomas lead a more aggressive course, and their five-year survival rate is reported to be only 11% (10). Some studies have demonstrated the association between the presence of vascular and lymphatic invasion, recurrence, and metastasis (11). Abnormal ploidy along with increased percentage of cells in S phase indicates lower disease-free survival and poor prognosis (12). Ki-67, showing proliferating cells in the tumor, is an indicator of early recurrence.

A majority of (70%) breast cancer patients have estrogen receptors. The estrogen-receptor-positivity rates have been reported as 80% and 60% in patients >60 and <40 years of age, respectively (8). The presence of receptor in the tumor affects the response to hormone therapy, thereby affecting the disease prognosis. Treatment approaches in breast cancer have been standardized based on the receptor status. While in the presence of estrogen and progesterone receptors, the response rates to hormone therapy have been indicated as 55-60% and 45-60%, respectively, it is reported to be only 8% in patients without estrogen or progesterone receptors (13). A 75-80% treatment response rate and improved prognosis are observed in patients having estrogen and progesterone receptors (14). Additionally, epidermal growth factor is negatively associated with estrogen-receptor positivity and is an indicator of poor prognosis (15). *P-53* gene controls DNA damage and prevents the replication of damaged DNA. This feature is not present in the mutant gene. While this characteristic is not seen in 27-62% of breast cancer patients (16), C-erbB-2 is detected in 20% of the patients with breast cancer. This protein is correlated with poor histological grade and lymph node involvement (17).

METHODS

In this retrospective study, the postmastectomy treatment results of 1,073 breast cancer patients who were admitted to our clinic between 1,987 and 1,991 were evaluated. The study being retrospective, no approval from ethics committee and informed consent from the participants were required. The patients in this study had right (n=529:49%), left (n=567:51%), and bilateral breast cancers (n=23:2%), and the study population consisted of postmenopausal (55%) and premenopausal patients (45%), and 16.5% of them were <35 years of age.

Table 1 presents the distribution of the patients according to histological characteristics, Table 2 shows the types of surgery, and the different stages of the surgery are presented in Graphic 1.

Of note, patients who had undergone breast-conserving surgery, which make up 20% of the patients, were not included in this study.

Radiotherapy: Postmastectomy, 835 patients (77%) underwent adjuvant radiotherapy. Of those, 50 Gy dose was delivered tangentially to the chest wall, supraclavicular, and the axillary region in 829 patients and 53-70 Gy doses to 6 patients. The remaining 238 patients (22%) did not receive radiotherapy.

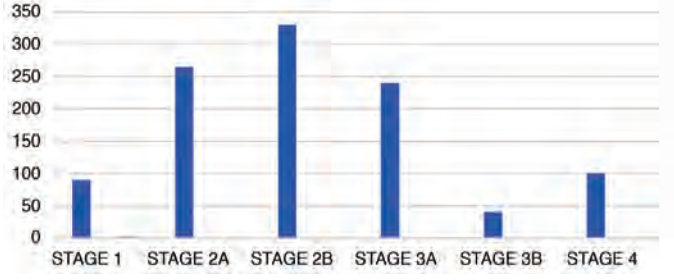
Chemotherapy: A total of 644 patients received adjuvant chemotherapy. Most frequently, a combination of CMF, was administered to 457 patients before and after radiotherapy for a total of six courses. F-cyclophosphamide-adriamycin or epirubicin combination was added to the risky patient groups.

Surgery: Of all the patients who underwent mastectomy, axillary curettage was not performed in 354 patients and 495 of them underwent inadequate axillary dissection. In addition, there was no pathological information about axillary involvement in 86 patients (Table 3).

Hormone treatment: A total of 804 patients used tamoxifen for 1-5 years. The receptor status of the patients was not determined in premenopausal patients before hormone therapy. Tamoxifen was administered to 92 postmenopausal and 16 premenopausal patients as an adjuvant monotherapy.

Table 1. Distribution by histology		
Histological characteristics	**n**	**%**
Ductal	1009	0.94
Invasive ductal	883	
Medullary	35	
Scirrhous	29	
Intraductal	22	
Mucinous	16	
Mixed	8	
Comedo	7	
Tubular	6	
Papillary	2	
Inflammatory	1	
Lobular	41	0.04
Paget's disease	4	0.003
Others	19	0.017

Table 2. Types of mastectomies		
Types of surgery	**n**	**%**
Simple mastectomy-axillary curettage	538	49
Modified radical mastectomy	395	36
Simple mastectomy	120	11
Radical mastectomy	43	4



Graphic 1. Distribution by stages

RESULTS

Local control: During the follow-up period of 84 months, local recurrence was detected in 67 (6%) and regional recurrence in 19 (2%) patients (3-60 months). Local recurrence developed in 27 (40%) premenopausal, 39 (58%) postmenopausal, and 1 pregnant patients. Regional recurrences, on the other hand, were detected in regions of ipsilateral axillary (n=4), ipsilateral supraclavicular (n=14), and mammaria interna (n=1). Of the 238 patients who did not receive radiotherapy, 49 developed locoregional and 40 local recurrences. Likewise, of the 835 patients who received radiotherapy, 37 developed locoregional and 30 local recurrences. Radiotherapy reduced locoregional recurrences by 5.6 times, thereby reducing locoregional relapses both statistically and significantly (p=0.0001) (Table 4). However, the difference in survival between these groups was not significant.

Distant metastases: Shortly after the onset of local recurrence, 40 (60%) out of the 67 patients with local recurrences developed distant metastases. Distant metastases were seen in the bone, lung, liver, brain, and soft tissue in 185 stage 3A and 94 stage 2B patients in the same order of frequency. Table 5 shows the relation between disease-free survival and survival rates and treatment outcomes.

Survival: The Cutler-Ederer method was used for the estimation of disease-free survival and survival analysis. Results were obtained after eight years of follow-up.

Table 3. Number of dissected lymph nodes		
Number of lymph nodes	**Patients**	
	n	**%**
0	354	27
1-3	306	18
4-7	189	30
8+	138	16
Unknown	86	9

Table 4. Effect of radiotherapy on locoregional control			
	Without radiotherapy	**Radiotherapy**	**p value**
Without loco/regional recurrence	79%	95.6%	0.0001
Locoregional recurrence	20%	4.3%	

Table 5. Treatment modalities and results			
	Patients number	**Disease-free survival**	**Survival rates**
General	1,073	73%	81%
Only RT +	77	76%	80%
RT -	238	65%	80%
RT + CT + TMX	758	75.5%	81%.5
Lymph node -	354	83%	88%
Lymph node +	619	69%	78%
Local recurrence	67	22.5%	54%
Distant metastasis	406	22.5%	45.5%
RT: Radiotherapy, CT: Chemotherapy, TMX: Tamoxifen			

DISCUSSION

Although the locoregional failure in patients undergoing surgery has been found to be at higher frequency compared to the patients who received postoperative radiotherapy, controversy about radiotherapy continues. While many studies have reported that breast cancer is a systemic disease from the beginning, and that local treatment will not be beneficial, it is important to improve the locoregional control and quality of life in a group of patients using radiotherapy.

Kae and Johansen (18) from Copenhagen compared the outcomes of radical mastectomy and radiotherapy applied after simple mastectomy in 715 patients, and after 15 years concluded that radiotherapy was more successful in preventing locoregional and distant metastases. In the first Stockholm Breast Cancer Study, the beneficial effects of pre- or postoperative radiotherapy were investigated, without any difference between both applications. However, locoregional success was reported to be better in patients undergoing radiotherapy (19). Moreover, in the combined results of the Oslo II and Stockholm Breast Cancer Studies performed to better evaluate patients who benefited from radiotherapy, it was reported that radiotherapy administration increased locoregional control and reduced distant metastases in 37% of the patients with axillary lymph node involvement (20).

On the other hand, it has been suggested that although radiotherapy may increase local control, when delivered especially to the left chest wall in cases of left breast cancer can result in cardiac deaths. Nevertheless, the rates of mortality due to cardiovascular diseases in patients undergoing postoperative radiotherapy at the Christie Hospital in England, after 14 years of follow-up, were lower than those seen in patients with local recurrence (21).

In the present study, local recurrence was observed in 21% (49 out of 238) of the patients who did not receive postoperative radiotherapy, while it was only 4% in (out of 848 patients) those who received radiotherapy. Radiotherapy therefore reduced locoregional recurrences by 5.6 times. Besides, locoregional recurrence was also statistically and significantly lower in those undergoing radiotherapy (p=0.0001). Additionally, distant metastasis developed in 60% of the patients who had local recurrences. This rate emphasizes the impact of local control on distant metastases. The survival rate of 76% in patients undergoing postoperative radiotherapy dropped to 65% when radiotherapy was not applied.

In 1995, the Early Breast Cancer Trialists' Collaborative group evaluated 17,273 patients from 36 different randomized trials and reported that postoperative radiotherapy increased local control three-fold compared to surgery but without any difference in 10-year survival rates (22). The presence and number of axillary lymph nodes involved were underlined so as to reveal the real beneficiaries from radiotherapy. Additionally, in their study, Valagussa et al. (23) demonstrated that relapses in Stage T1 breast cancer patients with axillary lymph node involvement were seen more frequently when compared with Stage 4 breast cancer patients without axillary involvement, and factors that are effective in locoregional success were also determined.

Further, in a radical mastectomy series followed-up for more than 50 years, Haagensen and Bodian (24) found local recurrences in 5%, 8-12%, and 20-42% of the patients with involvement of <4, 4-7, and >8 axillary lymph nodes, respectively, and recommended radiotherapy in patients with >4 axillary node involvement. Similarly, in the Oslo II study, it was seen that in patients with >4 axillary lymph node involvement and inner quadrant breast cancer, radiotherapy was more successful in increasing local control and preventing distant metastases (25). Interestingly, Fletcher et al. (26), in their study between the years 1963 and 1977, investigated 941 patients with axillary involvement and found that the 10- and 20-years survival rates were 55% and 50%, respectively, in 70% of their patients who received radiotherapy. When 1-3, and >4 lymph nodes were involved, the 10- and 20-year survival rates were reported as 50% and 48%, respectively. In patients with more >4 lymph nodes, recurrence was found most frequently in the chest wall.

When the relationship between axillary involvement and local recurrence was evaluated in our clinic, local recurrence was observed in 28% of the patients with 4-7 lymph node involvement, while it was 27% in patients without axillary

involvement. This high rate suggests that insufficient number of axillary lymph nodes were removed and correct staging could not be performed.

Furthermore, the Danish Breast Cancer Study Group has reported that the survival rates increase as the number of investigated axillary lymph nodes increase. According to their study, a significant difference in the survival rates were seen between the patients in whom more than and less than 10 axillary lymph nodes were removed (27).

Although the increasing effectiveness of radiotherapy in patients with axillary lymph node involvement has been demonstrated, the opinion that it adversely affects survival has been entertained for years. Cuzick et al. (28) in their meta-analysis evaluated eight studies and reported that the survival was worse in patients who received radiotherapy to their chest wall and those who were followed-up for 15 years; however, the cause could not be determined.

In order to be able to demonstrate that a treatment modality is effective, there should be a risk of recurrence of the disease in that area. However, radiotherapy was applied to all operated patients without staging in the first radiotherapy studies; therefore, the contribution of radiotherapy to local control could not be demonstrated.

In 1994, Cuzick et al. (29) reported that their meta-analysis was not valid, and neither were those reported in Oslo II, Heidelberg, and I. Stockholm studies. They reported that radiotherapy could cause cardiac toxicity due to technical reasons and high energy applications. Cuzick et al. (29) also demonstrated that reducing cardiac morbidity could contribute to survival.

On the other hand, chemotherapy has become a standard postoperative application since 1970s. However, it has been shown that the success rates of chemotherapy or radiotherapy alone cannot be more than the results obtained with their combination. Sykes et al. (30) applied doxorubicin and cyclophosphamide after mastectomy to 400 stage 2-3 patients, and added radiotherapy to 38% of patients. The local recurrence rate was 15% in the group of patients who received only chemotherapy, which was twice the number of patients treated with radiotherapy.

Griem et al. (31) from the Dana Farber Institute reduced the local recurrence rate to 20% in risky breast cancer patients when only chemotherapy was applied; however, local recurrence rate dropped down to 2% when chemotherapy was combined with radiotherapy.

In the Stockholm Breast Cancer Study II (32), CMF was compared with postoperative radiotherapy, and it was demonstrated that in postmenopausal women, radiotherapy increased disease-free survival, and at the same time decreased the rates of distant metastases in both post- and premenopausal women. Further, Fowble et al. (33) evaluated patients with 4-7 axillary lymph node involvement and tumors over 5 cm and reported that radiotherapy in combination with chemotherapy would contribute to local control and survival.

Although the contribution of radiotherapy to locoregional control was shown in these studies, its contribution to survival could not be demonstrated. The Danish Breast Study Group compared chemotherapy with chemotherapy plus radiotherapy in 1473 stage T3-4 risky breast cancer patients. Local control rates increased from 47% to 54% and survival rates from 63% to 68% in patients who underwent special treatment planned with the aid of tomography. The increase in survival rates was significant in patients with premenopausal patients with involvement of >4 axillary lymph nodes (34).

CONCLUSION

Radiotherapy delivered after mastectomy in breast cancer patients with involvement of >4 axillary lymph nodes and breast tumors >5 cm decreases local recurrence rate from 20% to 5%, and that increased local control also contributes to survival by lowering the rates of metastasis. In our patients, treatment was planned according to postoperative pathology reports, and thanks to radiotherapy applied to patients with axillary lymph node involvement, a five-year local recurrence, rate of 6%, and a highly increased survival rate of 88% were achieved.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: The study being retrospective, no approval from informed consent from the participants were required.

Peer-review: Externally peer-reviewed.

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

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ORIGINAL ARTICLE

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Relationship Between the Presence of Mental Retardation in Pediatric Patients Undergoing Elective Surgery and Preoperative Parent's Anxiety

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Abstract

Objective: The care of pediatric patients with mental retardation (MR) who will undergo surgery for families may become complex and stressful. This study aimed to investigate the effect of MR grade on the anxiety of parents of pediatric patients who will undergo surgery under general anesthesia.

Methods: The parents of 40 pediatric patients with group MR and 60 pediatric patients with normal mental state (group NMS) who underwent surgery under general anesthesia were subjected to preoperative State-Trait Anxiety Inventory (STAI) test. In addition to parents' demographic data, such as age, sex, educational status, occupational status, and consanguineous marriages, the effect of sex and MR grade of children on anxiety was examined.

Results: The patient's demographics showed nonsignificant differences. No significant difference was found between the parents of the two groups in terms of SAI and TAI scores. Similarly, parental occupation, education level, and sex of the child had no effect on the SAI and TAI scores. The presence of consanguineous marriages was significantly higher in group MR. In group NMS, a significant positive correlation was found between SAI and TAI scores of the parents.

Conclusion: No correlation was found between the presence and MR grade of the child and parents' SAI and TAI scores. Therefore, no relationship was found between MR in children and parental anxiety levels.

Keywords: Parental anxiety, mental retardation, pediatric anesthesia, minor surgery, State-Trait Anxiety Inventory

INTRODUCTION

Anxiety is a normal part of life. It allows us to be prepared to deal with daily problems, to make quick decisions in case of danger, and to avoid dangerous situations. Normally, this type of anxiety is mild and manageable (1). By contrast, excessive anxiety adversely affects daily life and even prevents an individual from continuing their normal activities.

Parents normally feel anxious when their children undergo surgery (2). Anxiety may develop in patients and/or parents in the preoperative period due to different reasons, such as fear of inability to wake up or of death after anesthesia, fear of loss of control, pain, isolation, separation from parents and separation from social life (3). Anxiety affects not only individuals who will undergo surgery, but also their family members (4).

Concerns about anesthesia and surgical intervention adversely affect surgery and postoperative recovery (5). Preoperative anxiety, postoperative behavior, and family anxiety are interconnected concepts that have gained great importance in recent years (6). Anesthesiologists are interested in the parents' emotional state as much as their patient's emotional state (7). Preoperative preparation of pediatric patients and prevention

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of anxiety are important parts of pediatric anesthesia. Anxiety in pediatric patients may cause negative postoperative behaviors, such as nightmares, isolation anxiety, eating disorders, and enuresis, and children's anxiety increases with the increase in parental anxiety (8). In the preoperative period, children and their parents should be psychologically evaluated together. The better the parents are prepared and informed in the preoperative period, the more they can help their children.

The care of pediatric patients with mental retardation (MR) is difficult in the normal period, and the management of the general condition of these children who will undergo surgery for families may become more complex. This may cause higher anxiety levels in families. In the literature, no study compared the preoperative anxiety levels of parents of children with MR and those of parents of children with normal mental state (NMS).

Therefore, this study aimed to investigate the effect of MR of pediatric patients who will undergo minor surgery under general anesthesia on parental anxiety. In addition, the association between demographic data, such as age, sex, education level, and occupation, and anxiety level were investigated.

METHODS

Our study was conducted in the operating room of the University of Health Sciences Bağcılar Training and Research Hospital after the approval of the Clinical Research Ethics Committee (decision no: 2018.05.02.049) and obtaining the written informed consent of all participating individuals. Parents of 40 pediatric patients with MR (group MR) and 60 pediatric patients with NMS (group NMS) who underwent elective surgery under general anesthesia in our hospital were subjected to State-Trait Anxiety Inventory (STAI) test. Parents who were illiterate or refused to fill out the questionnaire were excluded. Parents of children who had no history of operation under general anesthesia, who would be operated under elective conditions, and who were accepted in pediatric age group according to their developmental stages as younger than 18 years were included.

The children were administered 0.5 mg/kg midazolam orally 15 minute before admission to the operating room. Parents were allowed to answer questions without being influenced and in a calm environment. The demographic data of the parents, such as age, education, occupation, presence of consanguineous marriage, and age and sex of the child were recorded. The parents who participated in the study underwent STAI test preoperatively. The SAI and TAI scores of the parents in groups MR and NMS were compared. Correlations between the SAI and TAI scores of the parents were investigated. The effect of sex, parental occupation and educational status, and MR grade (mild, moderate, severe), determined by the child's medical report, on the SAI and TAI scores were also evaluated.

Statistical Analysis

Statistical analysis was performed with Number Cruncher Statistical System 2007 Statistical Software (Utah, USA). In the evaluation of data, in addition to descriptive statistical methods (mean, standard deviation), One-Way analysis of variance was used for comparisons between groups with normal distribution, independent t-test for comparison of two groups, chi-squared test for comparison of qualitative data, and Pearson correlation test to determine the relationships between variables. Moreover, $p<0.05$ was considered statistically significant.

RESULTS

The study included 100 patients, including the parents of 40 pediatric patients with MR (group MR) and parents of 60 pediatric patients with NMS (group NMS) were included in the study. Table 1 shows the demographic data of the groups. The rate of consanguineous marriages was significantly higher in group MR ($p=0.02$). No significant difference was found in the demographic data between the groups (Table 1).

No statistically significant difference in the mean SAI and TAI scores was found between the parents of both groups ($p>0.05$; Table 2).

Based on the child's sex, no effect was found on the SAI and TAI scores of the mother ($p=0.099$; $p=0.940$) and father ($p=0.294$; $p=0.643$) in group MR. Similarly, no statistically significant difference was found in the SAI and TAI scores of the mother ($p=0.633$; $p=0.576$) and father ($p=0.930$; $p=0.365$) in group NMS. With regard to the educational level of the parents, no significant differences were found in the SAI and TAI scores of the parents of both groups ($p>0.05$). With regard to the parents' occupation, no significant difference was found in both scale scores of the parents in both groups ($p>0.05$). No statistically significant difference was found between the mean SAI and TAI scores of the parents and MR grade (mild, moderate, severe) of the patients in group MR ($p>0.05$; Table 3).

No statistically significant correlation was found between the mean SAI and TAI scores of the parents in group MR ($p>0.05$). A statistically significant positive correlation was found between the mean SAI and TAI scores of the parents in group NMS, suggesting that parents in this group contribute to each other's anxiety in the preoperative period (Table 4).

Table 1. Comparison of the demographic data of the groups				
		Group MR (n=40)	Group NMS (n=60)	p
Mother				
Age		39.92±8.72	37.55±5.83	0.109
Education	Literate Primary school High school University	4 (10.00%) 24 (60.00%) 10 (25.00%) 2 (5.00%)	0 (0.00%) 36 (60.00%) 18 (30.00%) 6 (10.00%)	0.073
Occupation	Housewife Government employee Self-employment Employee	36 (90.00%) 2 (5.00%) 0 (0.00%) 2 (5.00%)	47 (78.33%) 5 (8.33%) 2 (3.33%) 6 (10.00%)	0.414
Father				
Age		43.78±9.3	41.42±5.26	0.116
Education	Primary school High school University	21 (52.50%) 16 (40.00%) 3 (7.50%)	20 (33.33%) 30 (50.00%) 10 (16.67%)	0.121
Occupation	Government employee Self-employed Employee Unemployed Retired	2 (5.00%) 19 (47.50%) 15 (37.50%) 1 (2.50%) 3 (7.50%)	10 (16.67%) 26 (43.33%) 23 (38.33%) 1 (2.50%) 0 (0.00%)	
Consanguineous marriages	No Yes	26 (65.00%) 14 (35.00%)	51 (85.00%) 9 (15.00%)	**0.02***
Children				
Age		10.5±3.78	9.58±3.01	0.182
Gender	Male Female	26 (65.00%) 14 (35.00%)	35 (58.33%) 25 (41.67%)	0.503

*Independent t-test and chi-squared test
MR: Mental retardation, NMS: Normal mental state

Table 2. Parental state and trait anxiety inventor scores			
	Group MR (n=40)	Group NMS (n=60)	p
Mother's SAI, median (min-max)	54.5 (31-72)	56.5 (31-75)	0.987
Mother's TAI, median (min-max)	46 (33-64)	48 (33-62)	0.344
Father's SAI median (min-max)	46.5 (30-70)	45 (28-76)	0.506
Father's TAI, median (min-max)	39.5 (25-56)	40 (32-73)	0.906

Independent t-test, SAI: State Anxiety Inventory, TAI: Trait Anxiety Inventory, MR: Mental retardation, NMS: Normal mental state, Min: Minimum, Max: Maximum

Table 3. Distribution of State and Trait Anxiety Inventory scores according to mental retardation grade				
	Mild mental retardation	Moderate mental retardation	Severe mental retardation	p
Mother's SAI Median (min-max)	56 (41-72)	53 (31-71)	59.5 (48-66)	0.292
Mother's TAI Median (min-max)	47 (33-61)	46 (36-59)	53.5 (43-64)	0.256
Father's SAI Median (min-max)	47 (30-70)	46 (33-64)	50 (38-68)	0.282
Father's TAI Median (min-max)	39 (25-54)	40 (30-52)	41 (38-56)	0.248

SAI: State Anxiety Inventory, TAI: Trait Anxiety Inventory, Min: Minimum, Max: Maximum

DISCUSSION

In our study, the STAI test was applied to the parents to evaluate the effect of MR in children who underwent minor surgery with general anesthesia on parental anxiety. The study results showed that MR in children had no effect of parental anxiety, and a

Table 4. Evaluation of correlation between State and Trait Anxiety Inventory scores of parents

Group		SAI (Mother)	TAI (Mother)
Group MR SAI (father)	**r**	-0.067	-0.048
	p	0.680	0.768
Group MR TAI (father)	**r**	-0.119	-0.169
	p	0.245	0.298
Group NMS SAI (father)	**r**	**0.288**	0.252
	p	**0.025**	0.052
Group NMS TAI (father)	**r**	0.145	**0.257**
	p	0.270	**0.048**

Pearson correlation test
SAI: State Anxiety Inventory, TAI: Trait Anxiety Inventory, MR: Mental retardation, NMS: Normal mental state

significant relationship was found between the presence of MR and consanguineous marriage.

Children undergoing surgery is a serious cause of anxiety for families. In the preoperative period, worries related to surgery and anesthesia cause anxiety in patients and their relatives, and this may lead to negative effects in the patient. Sime (9) reported that high anxiety level prolongs hospital stay, necessitates a higher dose of analgesics and sedatives, and increases the risk of postoperative complications. The anxiety of the parents, especially the mothers, contributes to the anxiety of children before they undergo surgery. The care of pediatric patients with MR is already difficult in the normal period, and it may be more difficult for families to manage their general condition preoperatively. This study aimed to compare the anxiety level of parents of pediatric patients with MR with those of pediatric patients with NMS. The literature reports variable results regarding the relationship between parent and child age with preoperative anxiety levels. Many studies reported that parental age has no effect on anxiety level (10-12). In a study investigating the relationship between maternal anxiety and child age, mothers of children younger than 1 year had higher anxiety levels (5). Güner et al. (13) obtained different results in their study, and no significant difference was observed in the anxiety level of parents when compared according to the age of the child. Because of the similar mean age of children and parents of the two groups, we speculate that these two variables did not affect our study results. In a study conducted in parents of children ≥2 years, the Beck anxiety scores were high, and no significant difference was found in STAI. In the same study, SAI scores were higher in the parents of girls compared with those of boys (14). In our study, no statistically significant difference was found between boys and girls in terms of parental anxiety. This difference between studies may be due to the different regions where the studies were conducted. In our country, cultural differences in different regions may cause changes in attitudes depending on the child's sex. Although no difference was observed in sex-related attitudes in some regions, girls or boys are given more importance or girls are more protected in some regions. Many studies have reported that anxiety levels are higher in women than in men (10,15-17). Badner et al. (10) found that the anxiety level of mothers of children who will undergo surgery was higher, and this increase was attributed to the high anxiety level of women due to separation from their families. Shevde and Panagopoulos (17) found a higher anxiety level in women, which was attributed to their ability to express their mood easier than men. In a study by Messeri et al. (18), STAI was applied to parents who were allowed to be in the operating room during anesthesia. In this study, anxiety levels of mothers were higher than those of fathers. In our study, no significant relationship was observed between the sex of the parent and anxiety levels in both groups.

In the literature, studies on the relationship between education and anxiety levels have yielded variable results. As the education level of the parents increased, TAI scores significantly decreased, and no difference in SAI scores was observed (13). Similarly, in another study, parents with university level had low TAI scores (14). However, in a study showing contrasting results, general anxiety level increased as education level increased (19). In addition to these contradictory results, some studies showed no correlation between anxiety scores and education level (5). In our study, no difference was found between SAI and TAI scores and educational level of the parents of both groups, which may due to the social norms and cultural impact in our society being more effective, regardless of education level, in our behaviors and perspective on events. There are limited studies in the literature examining the effect of parental profession on parental anxiety. Şenol (14) found that the anxiety level of the mothers who were housewives or belonging to lower occupational groups was higher, and they thought that this high level could be due to livelihood anxiety and stress factors. Similarly, in another study, the anxiety levels of mothers who were unemployed, housewives, or parents in lower occupational groups were higher than those in the middle and upper occupational groups (12). Our study found no statistically significant difference between the anxiety levels in the parents of both groups in different occupational groups, showing that our perspective on events is independent of education and profession. Our study found a statistically significant positive correlation between SAI and TAI scores of

the parents in group NMS, showing that the parents in this group contributed to each other's anxiety levels. By contrast, no correlation was found between the parents in group MR.

Rates of consanguineous marriages remain at high levels in our country despite knowledge of its disadvantages. As a result of consanguineous marriage, the risk of developing many diseases, such as phenylketonuria that causes MR in children, increases. In our country, the rate of consanguineous marriages is still higher than the world average, and this situation causes hereditary transmission of MR diseases in children. In our study, consanguineous marriage was found in 14 of 40 patients in group MR and 9 of 60 patients in group NMS. The rate of consanguineous marriages was significantly higher in group MR, which support the idea that the risk of developing MR diseases in consanguineous marriages is high.

CONCLUSION

No significant correlation was found between MR and MR grade of the child and the parents' SAI and TAI scores in our study. Therefore, no relationship is observed between MR and parental anxiety levels. In addition, a positive correlation was found between SAI and TAI scores of the parents of patients with NMS, suggesting that parents in this group affected each other both in normal life and under stress conditions.

Ethics

Ethics Committee Approval: Our study was conducted in the operating room of the University of Health Sciences Bağcılar Training and Research Hospital after the approval of the Clinical Research Ethics Committee (decision no: 2018.05.02.049).

Informed Consent: Written informed consent of all participants was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.E.C., Concept: S.D., F.G.Ö., A.S., Design: Y.E.C., S.D., F.G.Ö., Data Collection or Processing: Y.E.C., Analysis or Interpretation: S.D., Literature Search: Y.E.C., S.D., A.S., Writing: Y.E.C., S.D., F.G.Ö., A.S.

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Ultrasound-guided Percutaneous Microwave Ablation of Small Renal Masses: Short- and Mid-term Results, Safety, Effectiveness, and Prognostic Contributions

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Abstract

Objective: This present study aimed to evaluate the short- and mid-term results and outcomes, efficacy, safety, and possible prognostic contributions of ultrasound (US)-guided percutaneous microwave ablation (MWA) treatment performed on small renal masses (SRM).

Methods: We retrospectively analyzed the patients who had undergone US-guided percutaneous MWA of SRM using both their patient files that contained all of the follow-up informations and all the radiological images on the local picture archiving and communication system between July 2016 and July 2019. Age and gender of the patients were recorded. The following data and parameters were also obtained: histopathologic type of the SRM, pre and postablative tumor size in three dimensions (width, length, and height), tumor localization, the ablation procedure data (patient position, time, energy, presence of repeated ablation, adjacent structures, usage of protective techniques such as hydrodissection), time of local recurrence, and renal function test and parameters (urea, creatinine, and glomerular filtration rate).

Results: Thirteen patients with thirteen solitary SRMs that were ablated using MWA under USG-guidance were found. We performed one session for six lesions (46%), two sessions for six lesions (46%), and three sessions for one lesion (8%). Mean ablation time for each session was 2.54 minutes (range: 1.5-4). We demonstrated a complete ablation, which is a primary success, in eleven patients (84%) in the first month control computed tomography imaging. Two residual tumors were detected in two patients (16%).

Conclusion: MWA for the treatment of SRM is an effective and safe method with high technical success and low complication rates and good short- and mid-term results and outcomes.

Keywords: Small renal mass, ultrasound, microwave ablation, minimal invasive, nephrectomy, percutaneous

INTRODUCTION

Regarding the current management of small renal masses (SRMs), which refers to tumors with sizes smaller than 4 cm, there are several treatment methods depending on the patient's condition and clinical status, including open, laparoscopic or robotic partial or total nephrectomy, percutaneous or laparoscopic thermal and non-thermal ablations (1). Radical nephrectomy has been accepted for many years as the gold standard treatment approach in the management of renal tumors including SRM (2,3). Due to the advances in surgical instruments and techniques, the fact that nephron-sparing surgery has similar functional and oncological outcomes in the treatment of renal tumors smaller than 4 cm (SRM) as radical nephrectomy has made this treatment approach to be accepted as the new gold standard in the treatment of SRMs (4-8).

While these developments were experienced in surgical treatment, a significant increase was observed in the incidental detection of these tumors in parallel with the technological developments in the field of radiological imaging (8).

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Moreover, with the advances in imaging methods that are used for the ablation guidance, minimally invasive local tumor treatments that began with alcohol injection, continue today with thermal ablation methods such as radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CA), and the non-thermal ablation method, which is irreversible electroporation (9-11). The current literature reports that the local ablative treatments showed similar oncological outcomes when compared to the surgical treatment methods. However, local ablative treatment methods had lower complication rates and superior outcomes in renal function protection (12-15). Shorter recovery times and hospital stays, being minimally invasive procedures, having a minimal risk on ischemic injury, and their nephron-sparing features, are some of the advantages of the local treatment options over surgery. Due to these described features and advantages, local ablative treatment choices offer curative nephron-sparing treatment in SRM, especially for the patients having comorbidities that make surgery impossible (16-20).

There are several articles regarding RFA and CA in the treatment of SRM under the guidance of cross-sectional imaging such as computed tomography (CT) and magnetic resonance (MR) imaging in the current literature. Nevertheless, there are limited data regarding the MWA of SRMs under ultrasound (US)-guidance (11). This present study aimed to evaluate the short- and mid-term results and outcomes, efficacy, safety, and possible prognostic contributions of US-guided percutaneous MWA treatment performed on SRM.

METHODS

This retrospective study was approved by the local ethics committee (Prof. Dr. Cemil Taşcıoğlu State Hospital, 48670771-514.10). Informed consent was obtained from all the patients. The authors confirm that the study was carried out in accordance with the Declarations of Helsinki.

Patient Selection

We retrospectively analyzed the patients who had undergone US-guided percutaneous MWA of SRM using both their patient files that contained all of the follow-up informations and all the radiological images on the local picture archiving and communication system between July 2016 and July 2019. All the patients were asymptomatic individuals with the coincidental detection of a SRM that was compatible with a T1 tumor according to their CT or MR images. T1 tumor was accepted as a tumor that was 7 cm across or smaller and was only present in the kidney with no spread to lymph nodes or distant organs. All the patients were technically appropriate for percutaneous MWA.

Microwave Ablation Procedure

All MWA procedures were performed percutaneously by a radiologist who was experienced in interventional radiology and performed more than 15 percutaneous thermal ablation treatment with using only US guidance under deep sedation. MWA systems were 15-gauge electrodes with 2.45 GHz Solero and Acculis MWA generators (Angiodynamics, New York, USA) in all the procedures. Aplio 500 US system (Toshiba Medical Systems Corporation, Tochigi, Japan) had been used with 3-6 Mhz convex or 4-9.2 Mhz linear array transducers for the ablation guidance. All the patients whose preparations were made before the procedure were positioned on a sterile table in prone, lateral decubitus, or modified decubitus positions in accordance with the procedure plan. Following the local anesthetic infiltration throughout the ablation tract, the MWA probe was advanced towards the center of the lesion. Once the active part of the ablation probe was positioned at the center of the targeted ablation zone, two interventional radiologists checked whether the lesion had been centralized or not from different planes using US probe maneuvers. After ensuring the correct position, the ablation was started with deep sedation. The ablation time and energy level were selected from the guide determined by the manufacturer and adjusted to fit the lesion size properly, including the safety zone which was at least 5 mm for each margin around the tumor. Midazolam hydrochloride (3-5 mg) and fentanyl citrate (100-300 µg) were administered intravenously for the deep sedation. Immediately after adequate sedation, the ablation process was begun. The ablation process was controlled by following the bubbles, indicating the ablation and spread throughout the ablation zone around the probe with dynamic USG imaging (Figure 1). When considering incomplete ablations like in the case of large tumors or tumors in challenging locations etc., it was tried to cover the all lesion by repositioning the ablation probe.

Patient Follow-up and Definitions

Immediately after the ablation process, all the patients were referred to their clinic's inpatient service to monitor their vital signs, blood parameters, and renal function tests during the post-procedural first day. Control CT or MR imaging with US were obtained for each patients to evaluate the presence early complications and major residual tumor at the end of the first day after the ablation. The cross-sectional imaging was performed with intravenous contrast material administration

depending on the kidney functions of the patients. Then, all the patients underwent contrast enhanced (CE) CT scans or dynamic CE MR imaging were performed quarterly in the first 2 years, and biannually thereafter for follow-up (Figure 2). Besides, diffusion-weighted (DW) MR imaging obtained at different b values and apparent diffusion coefficient maps created from these data were added to the MR controls. In the first month control, the area with contrast enhancement on CE CT or MR images and/or the diffusion restriction on DW MR images were considered as the presence of a residual tumor due to incomplete ablation. Otherwise, the ablation was accepted as complete and successful. Local recurrence was defined as the ablated area with new contrast enhancement and/or the diffusion restriction on DW MR images in any of the follow-up period longer than three months (Figure 3). Patients with the incomplete ablation and local recurrence underwent a new MWA session.

Data Obtaining

Age and gender of the patients were recorded. The following data and parameters were also obtained: histopathologic type of the SRM, pre and postablative tumor size in three dimensions (width, length, and height), tumor localization, the ablation procedure data (patient position, time, energy, presence of repeated ablation, adjacent structures, usage of protective techniques such as hydrodissection), time of local recurrence, and renal function test and parameters [urea, creatinine, and glomerular filtration rate (GFR)]. According to the growth pattern and tumor localizations, the lesions were classified into four groups (Figure 4). In CT images of the day after the procedure, the subcutaneous tissue thickness from the anterior part of linea alba at the L3 vertebral body level was measured and grouped in 0.5 cm intervals to evaluate the effect of body mass by means of fatty tissue. To evaluate the impact of the interventional radiologist's experience, the MWA procedures were grouped into year ranges based on the first renal microwave procedure in 2016.

Statistical Analysis

Continous and categorical variables were presented as median (IQR) and number (%). Mann-Whitney U test, chi-square test, or Fisher extact test were used to compare the differences between the groups. An overall p value of less than 0.05 was as a statisfically significant result. Statistical analysis was performed with Statistical Package of the Social Sciences (SPSS) version 22.0 (IBM Corp.).

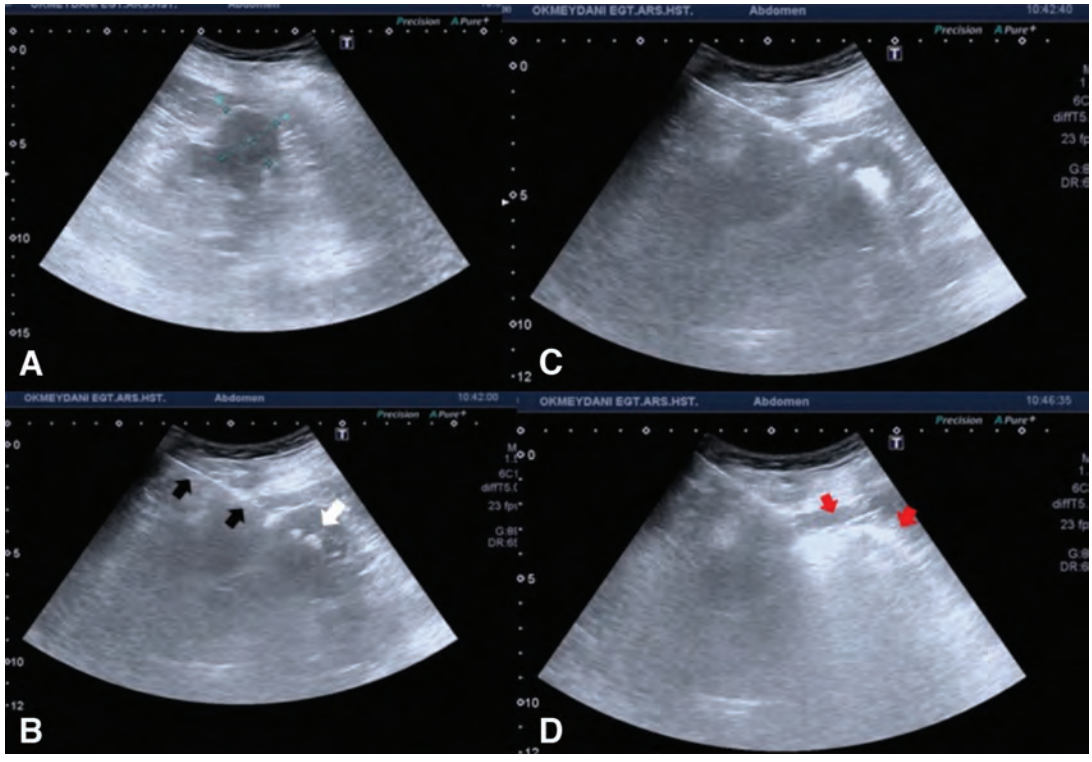

Figure 1. Ultrasound-guided microwave ablation procedure of a small renal mass. The lesion localization is in the middle part of the kidney with the exophytic morphology (A). Ablation probe's (black arrows in B) active part is positioned at the center of the targeted ablation zone and after ensuring the correct position, the ablation is begun with the bubbles (white arrow in B) which indicate the ablation process (B, C). Covering the all lesion with bubbles (red arrows in D) at the end of the targeted ablation time

RESULTS

Patient Population and Lesion Classifications

Thirteen patients with thirteen solitary SRMs that were ablated using MWA under US-guidance were found. Of these patients, seven patients were females and six were males. The mean age of the patients was 75.38 (range; 48-86 years) (IQR: 72-80). The histopathologic types of the tumors were detailed in Figure 5. Twelve patients had inappropriate conditions for surgical treatment due to a high risk of undergoing surgery and anesthesia, poor and limited renal function, and clinically important comorbidities. One patient having a history of Von Hippel-Lindau Syndrome underwent a previous partial neprectomy surgery on the contralateral kidney.

The mean longest diameter of the lesions was 33.53 mm (range; 28-50 mm) (Figure 6). Of the thirteen lesions, four lesions (31%) were in the exophytic, four lesions in the parenchymal (31%), and five lesions (38%) in the exophytic parenchymal location (Figure 4, Figure 7). Distribution of the lesions according to the longest diameter, the categorization of the subcutaneous tissue thickness, and the distribution of the lesions related to the interventional radiologist's years of experience are summarized in Table 1-3, respectively.

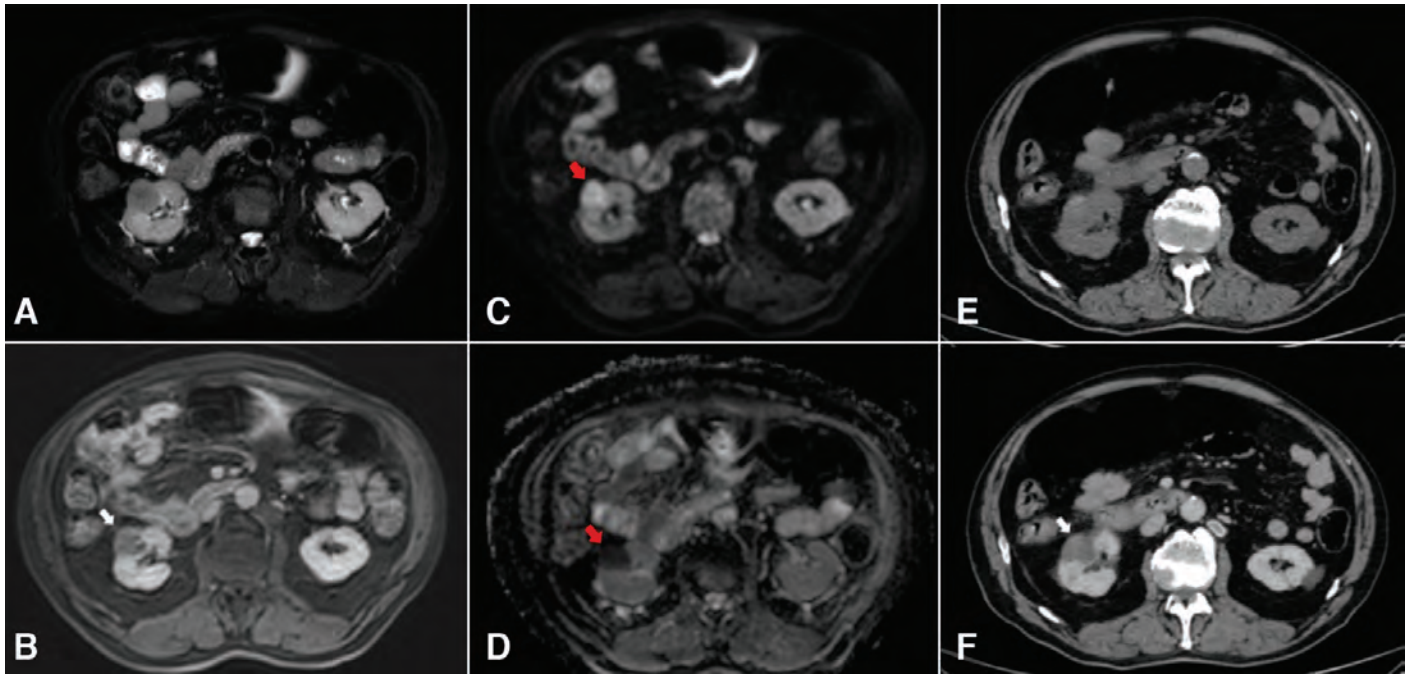

Figure 2. Contrast enhanced (CE) magnetic resonance (MR) images before the procedure (A-D) and follow-up CE computed tomography (CT) images (E, F). Well-demarcated SRM that was showing peripheral contrast enhancement and exophytic parenchymal localization in the right kidney (white arrow in B). The lesion showed diffusion restriction in diffusion weighted MR images (red arrows in C and D). In her first month follow-up, CE CT images demonstrated the ablation zone with no evidence of a residual tumor, compatible the complete ablation (white arrow in F)
SRM: Small renal masses

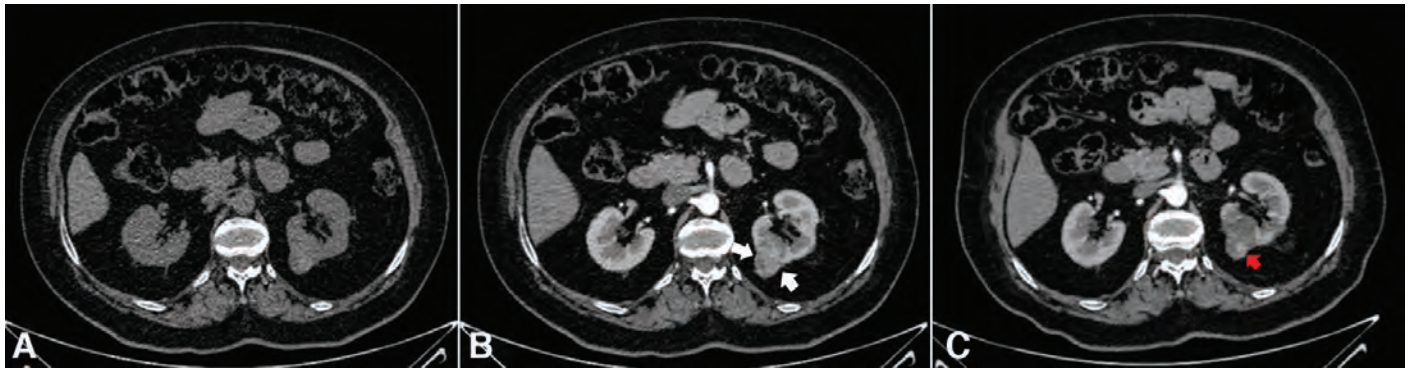

Figure 3. Dynamic contrast enhanced (CE) computed tomography (CT) images of a 69-year- old female patient with a small renal mass in the left kidney. Axial CT images before (A) and after (B) intravenous contrast administration show the exophytic parenchymal mass lesion (white arrows in B). In her first month follow-up CE CT, nodular residual lesion (red arrow) was demonstrated in the posterior part of the ablation zone (C)

Microwave Ablation Procedure

Among the thirteen patients with the thirteen SRM, we performed one session for six lesions (46%), two sessions for six lesions (46%), and three sessions for one lesion (8%). Thus, twenty-one ablation sessions were performed in thirteen SRMs. The mean energy level applied to the lesion during the ablation period was 109 watts (range; 80-140) per session. Since there was no finding to terminate the ablation in any patient, ablation procedures were continued till the specified target times were reached in all the patients. Mean ablation time was 2.54 minutes (range; 1.5-4) for each session. We demonstrated a complete ablation in eleven patients (84%) in first month control CT imaging as a primary success. In this first follow-up CT, since two residual tumors were detected in two patients (16%), new ablation sessions were planned to achieve the complete ablation. After the completion of ablations with mean ablation time of 2.5 minutes and mean energy level of 90 watts, secondary success was obtained as 100%. Since there was no endophytic lesion or the lesion with adjacent organ proximity less than 5 mm, asisted tecniques such as cold pyeloperfusion and hydrodissection that are used to prevent the pelvicalyceal system or adjacent structures from the non-target ablation were not performed in any procedure. Two (16%) lesions with residual tumor after the first ablation session were located in the exophytic parenchymal site (Table 4). The features of the lesions with residual tumors are presented in Table 5. Technical success rates were 83% (n=5/6), 83% (n=5/6), and 100% (n=1/1) for one ablation, two ablations, and three ablations in a single session, respectively.

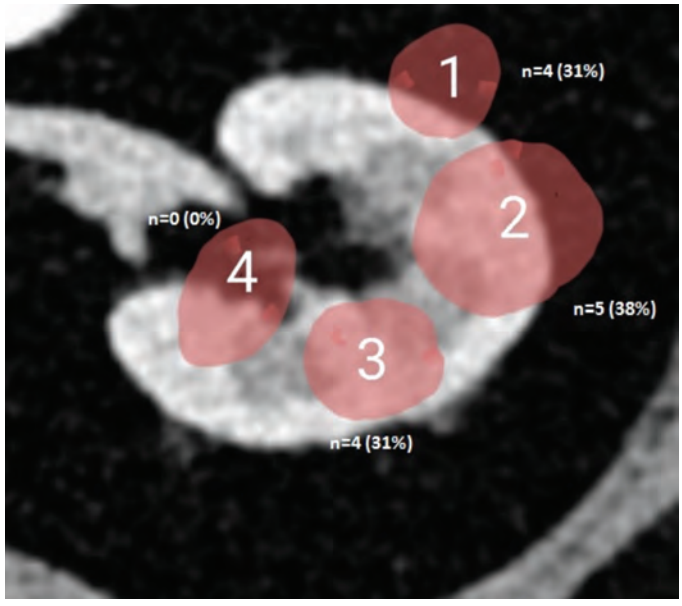

Figure 4. Classification of the tumor localizations according to growth patterns. Exophytic (1), exophytic parenchymal (2), parenchymal (3) and endophytic (4) patterns of the localization

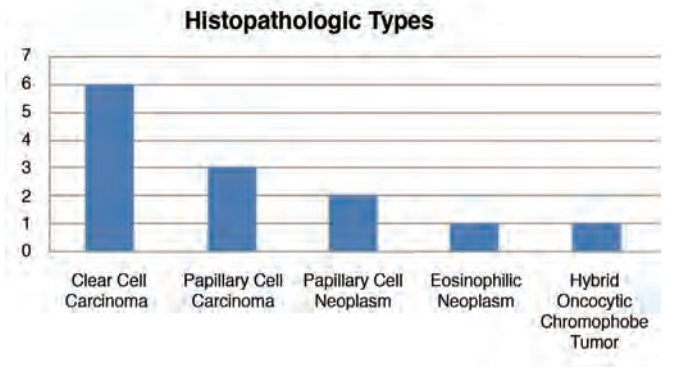

Figure 5. The histopathologic types of the ablated small renal masses

Table 1. Relationship between the longest diameter of the small renal mass and the presence of a residual lesion

Longest Diameter (cm)	Residual lesion		Total	p value
	No	Yes		
2-3	4	0	4	0.590
3-4	6	2	8	
4-5	1	0	1	
Total	11	2	13	

Patient Follow-up

The mean follow-up period after the successful procedures was 26 months (range; 5-46). One patient died due to myocardial infarction in the 5th month of follow-up regardless of the

Table 2. Relationship between the years of experience of the interventional radiologist and the presence of a residual lesion

Years of Experience	Residual lesion		Total	p value
	No	Yes		
0-1	2	0	2	0.244
1-2	4	0	4	
2-3	5	1	6	
3-4	0	1	1	
Total	11	2	13	

Table 3. Relationship between the subcutaneous tissue thickness and the presence of a residual lesion

Subcutaneous tissue thickness (cm)	Residual lesion		Total	p value
	No	Yes		
1-1.5	2	0	2	1.0
1.5-2	4	1	5	
2-2.5	2	0	2	
2.5-3	2	0	2	
3-3.5	1	1	2	
Total	11	2	13	

procedure and renal mass. When this patient was excluded, the mean follow-up period was revised as 27.8 months (range; 11-46). The follow-up periods were less than one year, between 1-2 years, between 2-3 years, and between 3-4 years in one patient (8%), three patients (23%), six patients (46%), and three patients (23%), respectively. General technical effectiveness and local tumor control rates were 100% with eleven lesions that were completely ablated in a single session, and two lesions with residual tumors that were completely ablated after a second session of ablation. Cancer-specific survival rate was 100%. One-year, two-years, and three-years of general survival and the disease-free survival rates were 100%, 100%, 92% and 100%, 100%, 100% respectively. There was no evidence of distant metastasis in any patients.

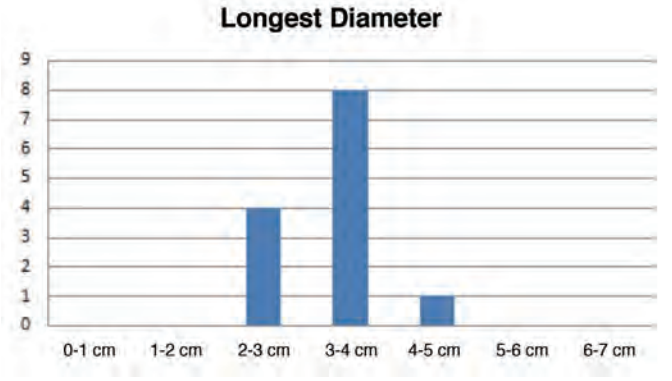

Figure 6. Distribution of the tumors according to longest diameter of the lesion

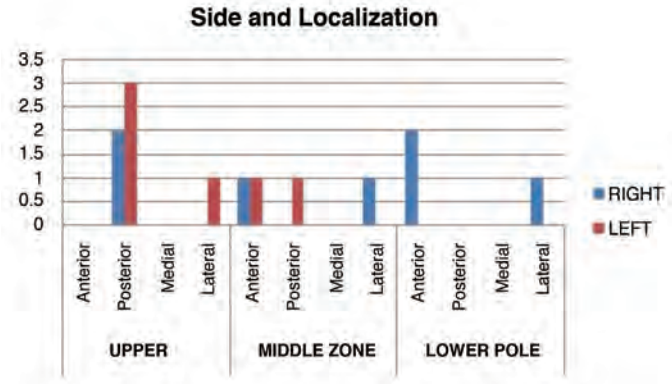

Figure 7. Distribution of the tumors according to the site and localization

Table 4. Relationship between the localization of the small renal mass and the presence of a residual lesion

Localization	Residual lesion		Total	p value
	No	Yes		
Exophytic	2	0	2	0.154
Parenchymal	4	0	4	
Exophytic parenchymal	5	2	7	
Total	11	2	13	

Complications

Only one patient developed a perinephric hematoma controlled by intravenous hemostatic therapy. After the hematoma was complicated with abscess formation, the patient was successfully treated by percutaneous drainage catheter placement under US-guidance and antibiotherapy. Apart from that, no major and minor complications occurred in any patient.

Renal Functions

Mean serum creatinine level was 1.07 mg/dL (range; 0.55-1.95) before the MWA procedure and 1.13 mg/dL (range; 0.6-2.36) one week after procedure. Mean estimated GFR (eGFR) level was 64 mL/min/m³ (range; 28-111) before the MWA procedure and 64.7 mL/min/m³ (range; 21-109) one week after procedure. In the follow-up examinations, a 20% increase was observed in the two patients' creatinine values, and these two patients were observed to be the ones with the highest creatinine values and the lowest eGFR values before the procedure. Including these two patients, no dialysis was required in any patient after the procedure.

DISCUSSION

Despite the well accepted surgical results and outcomes of partial nephrectomy, advances in imaging techniques and medical technology have brought the increasingly frequent use of thermal ablative treatments as an alternative curative method to surgical tumor excision, which is more conservative and minimally invasive in the treatment of SRM (20). Additionally, some advantages of these treatment methods such as having less complication rates than surgical treatments, shorter recovery times and hospital stay, not causing ischemic damage to the kidney, and most importantly, offering curative and nephron-sparing treatments to patients who are not suitable for the surgical treatments, increased their use in routine practice (16-20).

It is stated in the urooncology guidelines that RFA and CA, which are the widely used thermal ablation methods, could be taken into consideration in the treatment of T1a renal masses. Although there are fewer studies about MWA in the treatment of SRM compared to RFA and CA, the technical success and safety of MWA has been defined (11). In our study, we demonstrated the efficacy of US-guided MWA with the results and follow-up data of thirteen patients who underwent SRM treatment using MWA. We defined the general and the secondary success rates as 100% and this result was found to be comparable to the results

Table 5. Features of the lesions with residual tumors			
Variables		**Lesion 1**	**Lesion 2**
Age	Years	69	75
Gender		Female	Male
Histopathologic type		Papillary carcinoma	Eosinophilic neoplasm
Kidney (L/R)		Left/Upper pole posterior	Right/lower pole anterior
Localization		Exophytic parenchymal	Exophytic parenchymal
Pre-ablative size (APxMLxCC)	Milimeter	30x24x21	37x32x32
Post-ablative size	Milimeter	24x15x26	38x32x38
Ablation time (1. session)	Minute	2	3/2
Ablation energy (1. session)	Watt	60	100/100
Number of ablation		1	2
Follow-up time	Month	11	25
Ablation time (2. session)	Minute	3	2
Ablation energy (2. session)	Watt	100	60
Number of ablation		1	1
eGFR (pre-ablative)	mL/min/m³	96	28
Serum creatinin (pre-ablative)	mg/dL	0.55	1.68
eGFR (post-ablative)	mL/min/m³	94	21
Serum creatinin (post-ablative)	mg/dL	0.58	2.15
Complications		No	No
L: Left, R: Right, eGFR: Estimated glomerular filtration rate			

reported in the literature (11,21-26). Although local recurrence after MWA treatment is a disadvantage compared to partial nephrectomy, the high success rate achieved by courtesy of its easy repeatability both during the procedure and during the follow-up is an important advantage (9,11).

Factors that may affect the results of MWA can be listed as follows: tumor size, tumor localization, ablation time, applied energy level, the surface area of the ablation prob's active tip, tissue resistance (27). Tumor size is a determining factor in the patient selection and prediction of the procedural success in MWA. While the complete ablation rate is reported to be approximately 85% in renal masses of 3 cm and smaller, this rate decreases as tumor size increases and the need for complementary MWA is reported to increase (11,16-23). Another important factor affecting the success of the procedure is the tumor localization. It is known that the complete ablation rate is higher in the first session in tumors that are far from the renal pedicle and collecting system, located in the posterior and exophytic site, in other words, non-vascular perinephritic tissue (16-20). In contrast with the literature data, two (16%) lesions with residual tumor after the first ablation session were located as exophytic parenchymal in our study. It was observed that histopathologic type, tumor localization, growth pattern, tumor size, total energy level during ablation process, interventional radiologist's experience, subcutaneous tissue thickness, and number of ablation in the first sessions did not show a statistically significant relatioship in terms of residual tumors in the present study.

Thermal ablation processes can be performed under the imaging guidance of US, CT, or MR. The selection of ablation method depends on the interventional radiologist's preference and expertise and the clinic's ability to access imaging facilities (11,12). Combined methods with CT or MR can also be used in real-time fusion imaging to guide and to monitor the tumor ablation procedures. The most important advantages of US is that it allows the insertion of ablation probes in real time and does not contain ionizing radiation. However, its high operator dependency, gas artifacts due to adjacent intestinal structures, and application difficulties in obese patients are known disadvantages of the US (11). In addition, it is not always possible to differentiate the parenchymal component of the tumor from the normal parenchyma in US-guidance (28-30). CT has some advantages over US, including its less operator dependency, no intestinal gas artifact, and clear view of the

adjacent structures in multiplanar reconstructed images (11). To the best of our knowledge, there was no literature data that compared US and cross-sectional imaging guidance. Due tot technical reasons related to anesthesia support in the CT unit, we performed the thermal ablation treatments of SRM under US guidance in our department. Although our general success rate is similar to data in the current literature, we think that the technical failure of the two residual tumors in our study was due to the feature of the US, which is the limitation in the differentiation of the tumor border and adjacent renal parenchyma since these lesions were in an exophytic parenchymal localization. Our claim is supported by the data that the exophytic parenchymal localization of lesions with residual tumors rather than the endophytic localization that was accepted as more likely in terms of residue and the time of the ablation processes were in the partially experienced years of the interventional radiologist. It is clear that there is a need for randomized controlled trials comparing CT, MR, and combined methods with US.

In retrospective cohort studies, MWA had early and mid-term results comparable to RFA and CA, and the 3- and 5-year disease-free survival rates were reported 93% and 88%, respectively (21,24-26,31-33). It is mentioned in a meta-analysis about the effectiveness of thermal ablative treatment methods that there was no difference between MWA and CA in terms of local or metastatic recurrence despite the larger tumor size in MWA than CA (33). Yu et al. (24) reported that the recurrence rate was 0-23% in the follow-up of tumors that have been successfully ablated at the first session. In our study, no evidence of local tumor recurrence or distant metastasis (0%) were found in an average follow-up period of 26 months congruently with literature data.

It was revealed that MWA was superior to other local ablative methods in T1b renal tumor treatment. When compared to RFA, shorter ablation times, lesser heat sink effect, and the ability to achieve larger ablation zones can be considered as the advantages of MWA. Also, Ahmad et al. (34) mentioned that MWA showed better results in reducing kidney damage and in tolerability compared to RFA and CA.

MWA is a minimal invasive treatment choice compared to surgery. However, there could be some minor and major complications after MWA as follows; perirenal hematoma, macroscopic hematuria, bleeding, infection, stenosis or fistula formation due to non-target ablation of pelvicaliceal system, adjacent organ damage, and the pain at the site of ablation (35,36). In these current series, complication rates were reported as 4.8%, which was less than half of the rates reported for partial nephrectomy (11%) (21). In our study, self-limiting perirenal hematoma that did not require transfusion was observed in one (7.6%) case and it was a little bit higher than the literature data.

The recent studies have shown that ablative treatment methods are superior to surgery in the protection of the kidney function (11,12,27). We demonstrated that there was no significant difference between pre- and post-ablative serum creatinine and eGFR values in the present study.

We had several limitations in our study. The first and main limitation was the small sample size. Because of this, we could not conduct the subgroup analyses and the comparisons including the size, histopathologic types, and the localization. Larger sample size with subgroup analysis including different localizations and tumor sizes are needed in future studies. The second is the retrospective design and the short follow-up time of the study. Randomized controlled prospective studies with longer follow-up times are required. Despite these, the limited experience of MWA treatment of SRM through the literature and usage of US-guidance are the superior features of our study.

CONCLUSION

MWA in the treatment of SRM is an effective and safe method due to its high technical success and low complication rates, its renal function sparing features and good short- and mid-term results and outcomes when compared to RFA and CA.

Ethics

Ethics Committee Approval: Retrospective study was approved by the local ethics committee (Prof. Dr. Cemil Taşcıoğlu State Hospital, 48670771-514.10).

Informed Consent: Informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: E.K., Design: S.A., E.K., Data Collection or Processing: S.A., E.K., Analysis or Interpretation: E.K., Literature Search: E.K., Writing: S.A.

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

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CASE REPORT

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OPEN ACCESS

Cornelia de Lange Syndrome with Hypernatremia: Two Case Reports

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Abstract

Cornelia de Lange syndrome (CdLS), is a genetical syndrome which can be seen as hereditary, or sporadically. Characteristical appearance is very crucial for diagnosis. Although almost all patient shave characteristical face appearance, depending on the severity of the cases, some accompanying symptoms could be skeletal and extremity defects, gastrointestinal system diseases, central nervous system anomalies and related diseases, genitourinary system anomalies, or heart defects, vision and hearing problems. In this paper, two patients with holoprosencephaly and recurrent episodes of hypernatremia are minded us to reconsider CdLS as a differential diagnosis of hypernatremia. We also point out some important steps in the treatment of the hypernatremia.

Keywords: Cornelia de Lange syndrome, hypernatremia, holoprosencephaly

INTRODUCTION

Cornelia de Lange syndrome (CdLS), also known as Brachmann de Lange syndrome, was first as reported by W. Brachmann in 1916, and it was described by CdLS in 1933 (1). CdLS has been defined as a syndrome that includes microcephaly, synophysis (lush and thick, curved eyebrows in the midline), long lashes, deep orbital arch, small and blunt nose, antevert nostrils, long philtrum, thin upper lip, wide-spaced small teeth, small chin, big ears, posterior or low anterior hairline, bushy hair, distinctive phenotypic features, mental retardation or learning disabilities, intrauterine growth retardation, prematurity, retardation of postnatal growth and development, developmental anomalies of hands and feet, widespread or regional hypertrichosis, heart defects, eye and genitourinary anomalies, hearing loss, gastro esophageal dysfunction (2,3). According to phenotypic properties, type 2, CdLS classic type (type 1) and mild type (type 2) have been identified. Type 2, which shows mild phenotypic characteristics, has a better prognosis than the classical type (2,4,5). Two cases presenting with hypernatremia and diagnosed with CdLS were presented here.

CASE PRESENTATIONS

Case 1

The eleven-month-old girl was admitted to the pediatric emergency outpatient clinic with symptoms of vomiting, coughing, wheezing and weakness. Twenty five-year-old mother's follow-up without problems as the first baby after 41 weeks of uncomplicated pregnancy by cesarean section and she weighted 4,000 gr. It was learned that she had a convulsion on the second day after birth and stayed in the neonatal intensive care unit for 2 months due to the neonatal jaundice.

When she applied to the clinic, the general condition was medium-bad, severe dehydrated appearance, turgor tone decreased, Glasgow Coma score 11, fever 37 °C, respiratory rate 50-55/min, pulse 146/min, blood pressure 60/45 mmHg, SpO_2=98 (% with

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21 O_2), and the capillary filling time was under 3 seconds. On physical examination, facial appearance characteristic of CdLS compatible with synophris, long eyelashes, blunt nose, antevert nose, big ears, low hairline, and bushy hair, small discrete teeth, micrognathia, hypertrichosis, transfers lines in palms were seen (Figure 1). Body weight 7.5 kg (<3 p), height 68 cm (<3 p), head circumference 42.5 cm (median of first age), pulse rate as 110 per minute and respiration rate as 23 per minute were measured. On arrival, the patient's routine laboratory tests received hemoglobin 8.5 g/dL (11 to 16 g/dL, hematocrit 34.3% (37-54%), leukocyte 33.000 µL (4-103 µL), platelet 601,000 mm^3 (100,000-300,000 mm^3), glucose 152 mg/dL (74-106 mg/dL), urea: 172 mg/dL (8.4 and 25.8 mg/dL) creatinine 1.76 mg/dL (0.31 to 0.98 mg/dL), sodium 186 mEq/L (136-146 mEq/L), potassium 6.6 mEq/L (3.5-5.1 mEq/L), C-reactive protein 40 mg/L (<5 mg/L), fractional excretion of sodium 0.14%, pH: 7.23 (7.35-7.45), pCO_2: 55 mmHg (35-48 mmHg), HCO_3 20 mEq/L (22.5-26.9 mEq/L), pO_2 55 mmHg (83-108 mmHg), base deficit -5 were detected in blood gas. The patient was admitted for further examination and treatment, and intravenous fluid treatment was initiated by admitting severe hypernatremic dehydration. Desmopressin HCl was started by considering the syndrome-induced central diabetes insipitus due to high urine output, hypernatremic dehydration attacks in the past history, low urine density and high sodium in the follow-up. On the third day of treatment, blood sodium, urea and creatinine values returned to normal limits. The patient was discharged after scheduled outpatient follow-up.

Case 2

A five-and-a-half-year-old girl was referred to the pediatric nephrology outpatient clinic due to an increase in serum sodium values. The patient was born from the first pregnancy of the 31-year-old mother, born with cesarean as 4.500 gr in the term, there was no kinship between the parents, and she was treated for hypernatremia at the centers where she applied due to complaints of fatigue, inability to move her feet, and tendency to sleep when she was four months old. It was learned that cranial computed tomography and magnetic resonance examinations revealed holoprosencephaly, that she was treated for hypernatremia in the intensive care unit of another hospital before she was admitted to our outpatient clinic and was discharged the day before.

Body weight was measured at 10,250 kg (<3 p), height 87 cm (<3 p), head circumference 46 cm (1.5 median median) pulse rate was 110 per minute and breath count was 23 per minute. In his physical examination, synophrosis, long eyelashes, blunt nose, antevert nostrils, big ears, low forehead hairline, bushy hair, small split teeth, micrognathia, hypertrichosis, and transverse lines were seen in the palm (Figure 2). There was no walking and speaking, but he could understand simple sentences. Oral

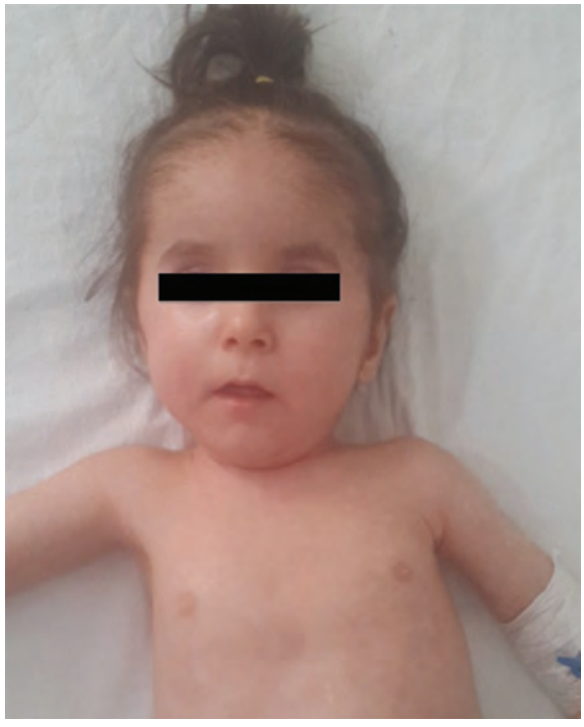

Figure 1. In case 1, Cornelia de Lange phenotypic features such as synophysis, long eyelashes, blunt snout, antevert nostrils, long philtrum, thin upper lip, wide-spaced small teeth, micrognathy, bushy hair

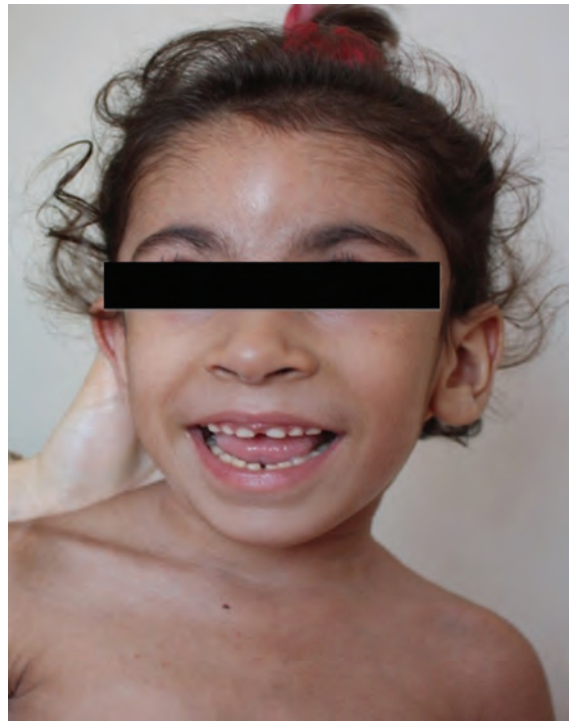

Figure 2. In case 2, Cornelia de Lange phenotypic features such as synophysis, long eyelashes, blunt nose, antevert nostrils, long philtrum, thin upper lip, wide-spaced small teeth, micrognathy, bushy hair

mucosa was dry, skin turgor was impaired and there were evident signs of dehydration. Mild tachycardia was present in the cardiovascular system examination. Respiratory system and abdominal examination were normal.

Serum sodium level 162 mEq/L (136-146 mEq/L), antidiuretic hormone (ADH) level 0.5 pmol/L (0.0-13 pmol/L) and creatinine level 0.55 mg/dL (0.31-0.98 mg/dL) were detected in laboratory studies. Urine creatinine levels were 127 mg/dL (40-278 mg/dL) and sodium 41 mEq/L (20-69 mEq/L). Fractional sodium excretion was 0.12%. Serum osmolarity was 335 mOsm/L (275-295 mOsm/L). With these findings, hypernatremia due to CdLS and prosencephaly were considered. Intravenous and oral fluid treatment was initiated and serum sodium values returned to normal limits on the second day of treatment. The patient has been discharged. Seven days later, when she came to the checkup, hypernatremia (serum sodium 162 mEq/L) was found to have recurred and the family did not provide the recommended liquid. The patient was again given intravenous and oral fluid treatment and serum sodium levels were restored to normal. The family was given genetic counseling, but genetic mutation analysis could not be done and the patient was discharged with oral hydration and serum sodium levels were stable during the sixth month of follow-up.

DISCUSSION

CdLS is a syndrome that is often diagnosed with characteristic facial appearance, and it is not common in the literature to have holoprosencephaly and surviving cases such as those presented in the case (3-6). Holoprosencephaly is an anomaly resulting from the inability of dividing the prosencephalon bilaterally to form the cerebral hemispheres. Patients with holoprosencephaly who have severe and complex anomalies die in the intrauterine period, and the incidence of living holoprosencephaly cases has been reported as 12/100,000 (2). Some of the complications of holoprosencephaly are adipsy, hypopituitarism, diabetes insipitus, neurogenic hypernatremia, and patients are therefore able to apply with the clinical picture of hypernatremic dehydration (7,8). Our patients also have hypernatremia episodes due to dehydration.

A mutation in the Nipped-B-like protein gene has been reported on the 5th chromosome in 50% of typical cases (type 1). Furthermore, the X-transitive form of the syndrome (type 2) has been reported to occur with a mutation in *structural maintenance of chromosomes protein 1A (SMC1A)* gene on the 10th chromosome, and the type 3 form has been reported to occur with a mutation in the *SMC3* gene on the 10th chromosome (9,10). For this reason, although chromosome and gene mutation analysis were not performed on our patients, families were given genetic counseling.

When plasma osmolarity in hypernatremia rises to 285 mOsm/kg, the first physiological response is increased ADH secretion and a feeling of thirst. These mechanisms do not work in infants, unconscious patients, or in cases where the brain does not develop, such as in our patients, so water retention or water intake in the kidneys can not be increased. When sodium intake increases, fractional sodium excretion icreases while hypernatremic dehydration decreases (11-13). In these cases, fractional sodium excretion of 0.14% and 0.12% support non-renal fluid loss. In hypernatremic dehydration, the clinical signs are mostly due to water and electrolyte imbalance between the body's liquid compartments. These patients are presented with various clinical statements such as convulsions, lethargy, hyperthermia, coma and encephalopathy. When sodium concentration is gradually increased in the blood, neurons synthesize a number of substances that raise intracellular osmotic pressure, called "idiogenic osmol", to prevent the loss of water going through the cell to the blood (12,13). Since serum sodium values were chronically high in our cases, serum sodium values reached 170 mEq/L, but central nervous system findings such as lethargy, coma were not observed.

Adipsy is a disease characterized by the absence of thirst sensation despite dehydration or excess of salt, which can be one of the rare causes of hypernatremic dehydration (11,12). The first physiological stimuli for thirst are increased osmolarity and hypovolemia. Osmoreceptors in the anterior wall of the third ventricle, the osmotic regulator of thirst, stimulate ADH secretion from the anterior hypothalamus. This warning is known as osmotic thirst. Any congenital or acquired lesion affecting the anterior hypothalamus or third ventricle can cause loss of sensation of thirst. These patients are presented with a combination of adipsy and central diabetes insipidus (11-13). ADH secretion may be unaffected, partially affected or completely affected in adipside. Rarely, some children may experience adipsia without a structural lesion. Although there was a structural abnormality in our cases, serum ADH value was within normal limits.

CONCLUSION

As a result, CdLS should be considered in patients with mental retardation, suspicious dysmorphic facial appearance and recurrent episodes of hypernatremia, care should be taken in their treatment and most importantly, the family should

be informed to ensure that the patient does not become dehydrated.

Ethics

Informed Consent: Oral consent has been obtained from the patient and her relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.D., Design: S.S., İ.B., Data Collection or Processing: H.D., E.K., Analysis or Interpretation: H.D., E.K., Literature Search: H.D., E.K., Writing: H.D., E.K.

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CASE REPORT

DOI: 10.4274/eamr.galenos.2019.16870
Eur Arch Med Res 2020;36(3):222-5

OPEN ACCESS

A Case of Parietooccipital Subdural Empyema After Spinal Anesthesia

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Abstract

Subdural empyema represents a loculated suppuration between the dura and the arachnoid. It has been described either intracranially or in the spinal canal and the latter localization is quite rare. It is a rare but serious disease with a decreasing mortality rate but rather common neurological sequelae. A high index of suspicion along with its typical clinical presentation such as headache, seizures, or focal neurologic signs can lead to early diagnosis so that effective treatment can be administered as soon as possible. Advances in the diagnosis and treatment of brain abscess and subdural empyema with neuroimaging techniques such as computerized tomography, magnetic resonance (MR) imaging, MR spectroscopy, the availability of new antimicrobials, and the development of novel surgical techniques have significantly contributed to the decreased morbidity and mortality associated these infections. Morbidity and mortality in intracranial and spinal subdural empyema are directly associated with the delay in administration of treatment. Both conditions should, thus, be treated with great urgency. In this case, we aimed to underline the possibility of intracranial subdural empyema occurence after spinal anaesthesia.

Keywords: Subdural empyema, spinal anaesthesia, fever, headache

INTRODUCTION

Subdural empyema is the accumulation of pus in the potential gap between the dura mater and the arachnoid membrane, and the most common cause is meningitis in children and sinusitis in adults (1-4). Like cranial epidural abscesses, most of the cranial subdural empyema is related to paranal sinusitis, otitis media, trauma and neurosurgical interventions. 50% of cranial subdural empyema cases can be detected with osteomyelitis or epidural abscess (5,6).

It constitutes 15-25% of all intracranial infections (1). Rapid diagnosis, surgical drainage and appropriate antibiotic treatment reduce mortality (7). The most common clinical triad is fever, neurological deficit and sinusitis. The findings such as headache, mental state change, fever, focal neurological deficit, vomiting, neck stiffness ease the diagnosis (2). In epidural abscesses, symptoms related to mass effect are in the foreground, while the patient may be in a toxic picture in subdural empyema. Clinically, it may be difficult to differentiate it from the brain abscess. Computed tomography (CT) or magnetic resonance (MR) are the methods to be chosen in the diagnosis (5,6). While complete recovery can be achieved with the proper treatment, there is high mortality or permanent neurological damage in case of delayed treatment or in untreated cases (1). The fact that the application findings are nonspecific in the early period, despite the advanced imaging methods, cause difficulties in diagnosis occasionally. Spinal subdural empyema is extremely rare. In treatment, empyema should be evacuated and antibiotic treatment should be administered, and antibiotic treatment should be continued for at least 3 weeks (5,6).

Here we present a subdural empyema case, a rare complication of spinal anesthesia.

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CASE PRESENTATION

An emergency caesarean section was performed due to acute fetal distress with spinal anesthesia in an eighteen-year-old, of ASA I physical group patient, whose consent was obtained, and is in the physical group, while there is not a feature in the anamnesis and laboratory tests. The patient had headaches occasionally, applied to several health centers, and no pathology was detected in the examinations. The patient had a fever, opened wound in the caesarean area, formication and numbness in the left arm and leg, it was evaluated as postpartum fever and antibiotherapy was initiated. In the neurology consultation of the patient whose complaints continue; general condition is good, conscious, direct and indirect light pupil reflex bilateral +/+, left upper extremity muscle strength -5/5, four extremity deep tendon reflexes were found normoactive. In cranial CT; minimal effusion at the subdural distance in the left occipital region and widespread edema in the left hemisphere were observed and acetylsalicylic acid 100 mg and low molecular weight heparin 0.6 were started primarily by considering venous thrombosis (Figure 1). The patient's complaints continued, in contrast cranial MR taken 2 days later; left hemispheric sulcus were cleaned, cerebral parenchyma has edema, 13 mm depth and 36x59 mm intense collection (empyema), contrasting at the subdural distance at left parietooccipital region, fluid collection in the sphenoid sinus, meningial and meningeal inflammation in left cerebral hemisphere, and accompanying cerebritis findings were detected.

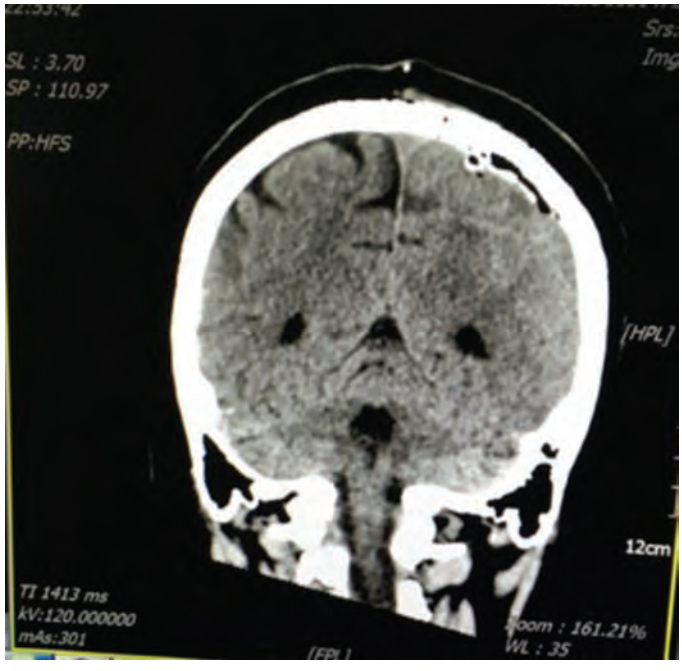

Figure 1. Cranial CT; minimal effusion at subdural distance in the left occipital region and widespread edema in the left hemisphere
CT: Computerized tomography

(Figure 2). After the emergency operation was planned, 2 *burr holes* opened following the control of bleeding in prone position under general anesthesia. Purulent material was evacuated and sent to the laboratory. Hemostasis was achieved, duraplasty was performed and tisseel was applied. One hemovac drain was placed at the epidural distance, the layers were closed proper to their anatomy (Figure 3). No postoperative complications developed, no transfusion performed. Since our case was initially evaluated as postpartum fever and antibiotherapy was initiated, there was no growth in blood, wound culture, and urine culture. Ceftriaxone disodium and metranidazole treatment were initiated with the recommendation of the infection committee. Infection parameters decreased in the following laboratory tests (C-reactive protein: 12, white blood cell: 7.32, hemoglobin: 11.3, procalcitonin: 0.03). Normal findings were detected in the non-contrast CT (Figure 4) in the early postoperative and 1st week, and then the patient, whose antibiotherapy continued, was discharged with healing.

DISCUSSION

In the presented case with the central nervous system infection, the cause of headache could not be found since there were no clinical and physical examination findings. With the precence of

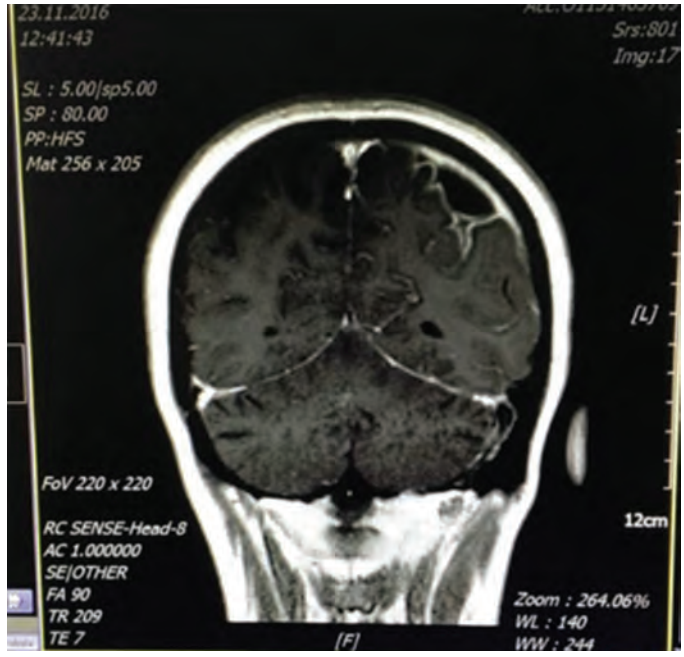

Figure 2. Cranial MR with contrast; left hemispheric sulcus deleted, cerebral parenchyma is edematous, 13 mm depth 36x59 mm intensive collection of contents involvement in left parietooxypital level subdural distance, sphenoid sinus fluid collection, menengial and menengial inflammation in the left cerebral hemisphere and accompanying cerebral findings
MR: Magnetic resonance

fever, the other factors that might cause fever were evaluated and it was diagnosed as postpartum fever and antibiotherapy was initiated. Central nervous system imaging was made and subdural empyema diagnosis was made due to severe headache, fever complaints in the application, and the first motor neuron findings in the neurological examination in our hospital.

Subdural empyema is a locular infection of the meninges between the dura and the arachnoid and may develop in the intracranial or spinal canal (1,2). Intracranial subdural empyema is often a complication of sinusitis or less frequently otitis or neurosurgical interventions (8,9). In the literature, subdural empyema due to spinal anesthesia only is limited to a few cases (10).

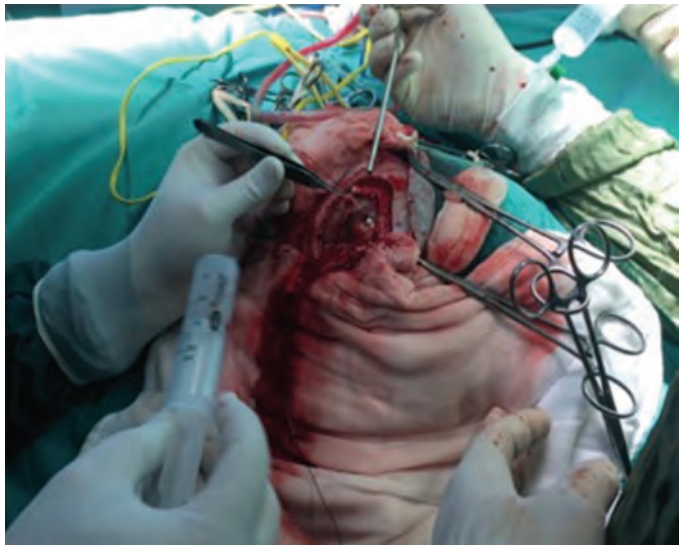

Figure 3. Intraoperative empyema discharge

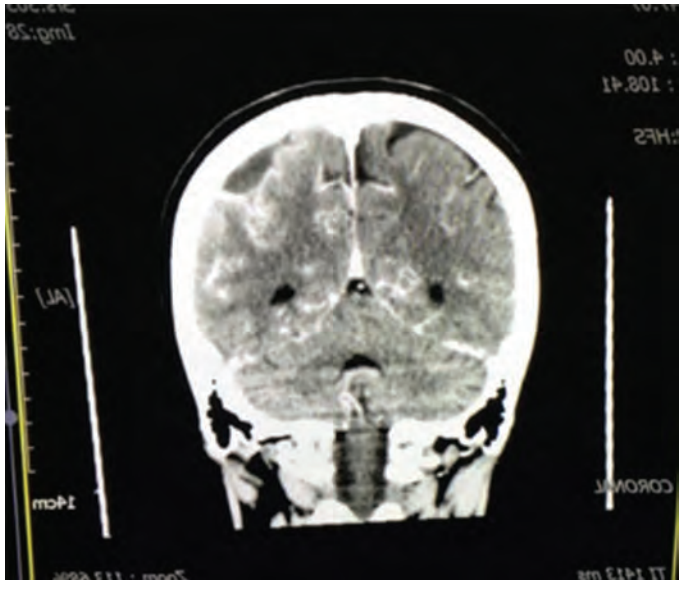

Figure 4. Non-contrast CT in early postoperative period
CT: Computerized tomography

In our patient, fluid collection was observed in the sphenoid sinus in MR. The developing subdural empyema may also originate from sinusitis, but the development of the clinical picture after spinal anesthesia, the initiation of antibiotherapy with a preliminary diagnosis of wound infection, worsening of findings and the diagnosis and treatment of sinus thrombosis complicated the case.

Recent epidemiological series in Europe suggest that the frequency of infectious complications associated with neuroaxial techniques may increase (11). The most common organisms in intracranial subdural empyema are anaerobic and microaerophilic streptococci (8). In the literature, isolation of rare microorganisms such as *Mycoplasma hominis* isolation from subdural empyema in culture biopsy material has also been observed. In the case that Delgado Tapia et al. (12) presented: in the 32-year-old patient who experienced throbbing-style headache 48 hours after cesarean delivery under spinal anesthesia, abscess was detected in the abdominal wall with worsening headache on the fifth day of the operation; despite antibiotic treatment, when fever and headache persisted, as in our case, subdural empyema was detected in cranial MR imaging and drainage was performed twice with emergency surgery. After the combination of surgery and antibiotic therapy, the patient was completely cured.

The diagnostic procedure selected for intracranial and spinal subdural empyema is CT, MR. CT scan may not identify intracranial subdural amps that can be detected by MR (13). As a matter of fact, venous thrombosis was considered primarily with CT findings in our case. In almost all cases of intracranial or spinal subdural empyema, rapid surgical drainage and antibiotic treatment are required. Pus in the empyema should always be sent for aerobic culture as well as anaerobic. Since intracranial subdural empyema may contain multiple organisms, temporary antibiotic treatment of intracranial subdural empyema, in which the organism is unknown, should be directed to *Staphylococcus aureus*, microaerophilic and anaerobic streptococci and gram negative organisms (1,14). Antibiotics; naphsilin, oxacillin or vancomycin; + third generation cephalosporin; it should contain + metronidazole. Temporary antibiotic treatment of spinal subdural empyema should be directed to *S. aureus* and *streptococci* and should include nafsilin, oxacillin or vancomycin (15). Morbidity and mortality in intracranial and spinal subdural empyema are directly related to the delay in planning treatment. Therefore, both conditions must be treated with urgency (1,16-19). Since our case was initially evaluated as postpartum fever and antibiotherapy was initiated, there was no reproduction in

cultures, an emergency operation was performed as soon as the diagnosis was made and the abscess was evacuated. Infection parameters decreased in the following laboratory tests.

CONCLUSION

As a result; in case of prolonged headache, fever, focal neurological finding after spinal anesthesia, the problem should be considered as it is more serious than expected and the focus of infection may be the central nervous system, empirical antibiotic treatment should not be initiated before the cause of the fever is fully clarified and careful neurological examination and radiological examination should be performed.

Ethics

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.M., B.S., C.P., A.Y.A., Concept: T.M., A.Y.A., N.T., Design: T.M., N.T., Data Collection or Processing: B.S., C.P., A.Y.A., Analysis or Interpretation: T.M., A.Y.A., N.T., Literature Search: T.M., B.S., C.P., A.Y.A., Writing: T.M., A.Y.A., N.T.

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

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CASE REPORT

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OPEN ACCESS

Primary Ovarian Leiomyosarcoma: A Case Report and Review of the Literature

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Abstract

Ovarian sarcomas represent less than 3% of all ovarian tumors. Leiomyosarcoma (LMS) is a rare subtype, accounting for only 0.1% of all ovarian sarcomas. We present a case of primary ovarian LMS in a 68-year-old multigravid woman. She was treated by total abdominal hysterectomy with bilateral salpingo-oophorectomy, followed by adjuvant chemotherapy. The prognosis of ovarian LMS is very poor. Although different treatment modalities like adjuvant chemotherapy and radiotherapy have been described, no clear benefit has been proven.

Keywords: Primary ovarian, leiomyosarcoma, sarcoma

INTRODUCTION

Primary ovarian sarcomas are rare gynecological tumors accounting for less than 3% of all ovarian tumors (1). Only a few cases of fibrosarcoma, leiomyosarcoma (LMS), carcinosarcoma, angiosarcoma and other histological types have been reported. Less than 0.1% of ovarian sarcomas are LMS (2-4). Because ovarian LMS are rare, there are not many case reports in literature, and no prospective studies for management recommendations. Therefore, optimal treatment guidelines have not yet been developed.

There is no treatment modality other than surgery, total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) for ovarian LMS (5). They are generally high-risk cancers and have a very poor prognosis. The type and utility of adjuvant therapy is controversial (6).

Here, we present a case of primary ovarian LMS in a postmenopausal woman presenting a giant abdominal mass.

CASE PRESENTATION

A 68-year-old multigravid woman presented to the gynecology clinic with complaints of abdominal pain and a palpable abdominal mass. Additionally, the patient had a history of hypertension. The patient's pregnancy history was G5 P5, her menarche age was 13 years, and her last menstrual period was 8 years ago, she was postmenopausal.

Physical examination revealed a mobile, hard mass of about 20 cm in diameter, which was palpable to the level of the umbilicus.

On abdominal ultrasonography, a 120x180 mm multilobulated cystic mass containing many septas and thick walls was seen posterior to the uterus; the origin of the mass could not be detected. Laboratory findings showed tumor (CEA, CA 19-9, CA 125, CA 15-3) and biochemical markers within normal limits. No malignancy was observed in cervical cytology, and histopathological result of endometrial sampling revealed atrophic endometrium.

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The patient was scheduled for surgery with a prediagnosis of degenerative leiomyoma. Intraoperatively, a solid cystic mass of about 20 cm in diameter arising from the left adnex adhered to transverse colon and left pelvic side wall. There was no evidence of right-sided and upper abdominal diseases, and no ascites. Cytology was taken by peritoneal lavage. Adhesiolysis with sharp dissection, TAH and BSO were performed. Intraoperative pathology consultation (frozen section) was demanded, and histopathological evaluation reported a mesenchymal tumor, which could not be distinguished as benign or malignant.

There were no abnormal findings for the first two postoperative days. A day later, the patient complained of abdominal distension, vomiting and nausea. Oral intake was stopped for two days and decompression with a nasogastric tube was done. On the fifth postoperative day, oral regimen was reinstated, and the patient's complaints regressed. She was discharged problem-free one week after surgery.

The histopathological result was left adnexal LMS. Macroscopically, the mass was gray-white, 20x13x11 cm in size, fibrillar in structure with nodular areas, and multilobulated. Microscopically, coagulative tumor necrosis, >10 mitosis per 10 high-power-fields (HPF), diffuse and severe atypia were seen. Cytological evaluation reported benign peritoneal cytology.

At the first month follow up examination, she had no complaints and no lesion was observed on abdominal computed tomography and positron emission tomography scan. Her CA 125 value was 12 μ/mL, and other tumor markers were equally within normal limits. Based on these results, the patient was referred to the department of medical oncology for consultation. They recommended four cycles of adriamycin chemotherapy.

DISCUSSION

Smooth muscle tumors of the ovary are uncommon, accounting for less than 1% of all ovarian tumors. These tumors originate from hilar blood vessels or smooth muscle metaplasia of ovarian stromal or theca cells (7). The most common primary ovarian sarcomas are fibrosarcomas, endometrial stromal sarcomas, carcinosarcomas and rhabdomyosarcomas (3). Primary pure ovarian LMS is a very rare tumor (8). In literature, there are some cases mentioned as ovarian LMS. However, the case series are few. Lerwill et al. (7) reported 54 ovarian smooth muscle tumors including 26 LMS.

Ovarian LMS occur typically in postmenopausal women, as in our case. Zygouris et al. (8) calculated a mean age of 52.6 years and He et al. (9) of 54.9 years. Despite this, several cases have been seen in adolescence (10,11).

Ovarian LMSs do not have specific symptoms. Patients may present with abdominal pain, weakness, postmenopausal bleeding, or a palpable abdominal mass, as in our case. The tumor is mostly seen as solid masses with or without cystic degeneration, based on imaging modalities.

Cases of primary ovarian LMSs are so rare that no recommended guidelines on optimal treatment have been established. The main treatment type is surgery which extends from fertility sparing to debulking surgery, consisting of TAH, BSO and excision of the tumoral masses (5,12). Although surgery was performed for all cases, the scope of surgery is controversial. Because the probability of occult metastatic disease is likely low, a second operation is not necessary for patients without lymph node dissection or omentectomy (5). There are different approaches in terms of surgery. In one instance, a 27-year-old patient who underwent complete surgical staging, followed by 6 cycles of gemcitabine-adriamycin chemotherapy had no evidence of recurrent disease over a period of 47 months (13). There are also cases in which TAH + BSO is performed, and adjuvant chemotherapy is given (14,15). In our case we performed TAH + BSO, no per operative palpable lymphadenopathy was found, postoperative imaging were normal, and histopathological findings were compatible with ovarian LMS. This was made of tumor cell necrosis, 23 mitosis per 10 HPF, and significant atypia microscopically (7). Immunohistochemical markers like desmin, vimentin, and smooth muscle actin could also be used in the diagnosis of ovarian LMS (1,6).

The prognosis of ovarian LMS is very poor. Although treatment modalities such as chemotherapy and radiotherapy have been described, there is no sufficient data to prove that such treatment will improve survival outcomes (5). The prognosis depends on the tumor size, stage and mitotic index (6). There are no prospective data supporting the routine use of adjuvant chemotherapy for disease limited to ovary (5). In our case, since the mitosis rate was high and the tumor size was large, the oncology department decided on adjuvant chemotherapy. Four courses of single agent (adriamycin) chemotherapy were planned. However, there is no evidence that chemotherapy will improve survival outcome. In our patient, the expectation of disease recurrence is high, and resection of recurrent tumor is recommended (5).

CONCLUSION

Ovarian leiomyosarcomas are rare tumors and have no established standard treatment. Surgery is thought to be the

main modality for treatment. Although chemotherapy and radiation therapy are used as adjuvants, there is no strong evidence that they have any additional benefits.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.K.E., Design: N.K.E., K.Ç., Data Collection or Processing: N.K.E., R.D., Analysis or Interpretation: N.K.E., K.Ç., C.R.A., Literature Search: R.D., Writing: N.K.E., K.Ç.

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

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

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CASE REPORT

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OPEN ACCESS

Top of the Basilar Artery Syndrome (Bilateral Thalamic Infarction) Observed After Cesarean Operation Under Spinal Anesthesia

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Abstract

Top of the basilar artery syndrome; is revealed as a result of the brainstem and lower cerebral, cerebellar area infarction due to the embolism of the basilar artery's most rostral part. It may present with very mild symptoms, leading to severe neurological sequelae or death. In this report, we present a case of bilateral thalamic infarction with no history of chronic disease.

Keywords: Basilar artery syndrome, pregnancy, bleeding

INTRODUCTION

Thalamus is the intersection of frontoparietal connections with memory systems such as the hippocampus and the limbic system (1). The basilar artery originates from the intersection of two vertebral arteries at the ponto-bulber junction and terminates at the pons-mesencephalon junction. Spinal anesthesia is one of the most common techniques used in anesthesia applications in obstetric patients, children, and ambulatory surgery patients, but it can cause a variety of neurological complications. The incidence of neurological complications associated with spinal anesthesia is 3.78 in 10,000, and some are permanent neurological deficits (2).

Basilar artery occlusion can cause very mild symptoms by embolizing the bilateral posterior cerebral artery and cerebellar arteries, as well as a wealth of neurological symptoms such as impaired consciousness and bilateral pyramidal, sensory, cerebellar findings, cranial neuropathies or conjugated gaze disorders. Mental state changes, vertical gaze limitation and memory impairment constitute the classic triad (3,4). Its prognosis is highly variable and depends on the location, spread and collateral circulation of the occlusion. The symptoms are sudden and dramatic, so the clinical picture should be immediately recognized and patients should be referred to appropriate treatment. Magnetic resonance imaging (MRI) and diffusion-weighted imaging play a key role in imaging because clinical findings are not leading in many cases. In this paper we present a case of bilateral thalamic infarction in a thirty-seven-year-old woman with no history of chronic disease on her resume.

CASE PRESENTATION

Thirty-seven years old female patient diagnosed with known chronic disease, miscarriage and no history of previous thrombosis. Four days ago, there is a history of cesarean section under spinal anesthesia for her second pregnancy and it is known that cesarean section in her first pregnancy took place uncomplicated under spinal anesthesia. The patient who was brought to the emergency department of our hospital after the development of confusion and tendency to sleep was interned to the intensive care unit (ICU) after spinal anesthesia

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upon the determination of acute lacunar infarction and left thalamic infarction in bilateral posterior comminican artery irrigation area on cranial diffusion MRI. The patient was treated with antiedema, antiagregan and anticoagulant. Physical examination at the time of hospitalization showed no signs of neck stiffness or meninx irritation, except for bilateral roncus in the basal lung. Arterial blood pressure: 110/70 mmHg, pulse: 76 beats/min, fever was 36.2 °C. Neurological examination revealed unconscious, Glasgow-Coma scale: 8, pupillary myotic-isochoric, LR +/+, eyes give on to right, response to painful stimulus in 4 extremities +, no lateralized signs, Babinski sign with flexor on the right and extensor on the left.

The patient who had bilateral infiltrative changes in the chest-X-ray was started to receive antibiotic therapy. Cranial diffusion MRI examination taken on the same day showed areas in favor of acute infarction showing symmetrical diffusion restriction in both pariyetooxypital, both occipital lobes and both medial temporal lobes. Acute infarction areas showing diffusion restriction were observed in bilateral thalamus and right half of pons. Cranial computed tomography (CT) showed large hypodens in the ponsta, both cerebral hemispheres, bilateral occipital lobes, both temporal lobes, bilateral thalamus, more prominent on the left. Both cerebral hemispheres appear to be edema, and as a result, cerebral cortical sulcuses have been wiped out. It has been observed that the third ventricle is semicomprese (Figures 1, 2). No pathological findings were observed in transesophageal echocardiography, bilateral lower limb venous Doppler and urinary ultrasonography examinations for etiological factors. Vasculitis and thrombosis panel were examined. ANA+, FANA (antinuclear antibody performance) + thin-spotted pattern, HLA B27 resulted in negative. Bilateral carotid-vertebral artery color doppler ultrasonography was observed to be compatible with vasculo biliary injury.

In the neurological examination of the patient, who was diagnosed with ischemic stroke (bilateral thalamic infarction) as a result of 1.5-month ICU follow-up; right-hand dominance (+), unconscious, no orientation and cooperation, no word output, comprehension was partially preserved, no stiff neck, Kernig (-), Brudzinski (-), light reflex direct-indirect were positive bilaterally, pupils were isochoric, conjugated eye movements were totally normal in all directions, no nystagmus, no facial asymmetry, the tongue was in the midline and outside the mouth, four limbs were spontaneously mobile, deep tendon reflexes were alive in the lower limbs, normative in the upper extremities, bilateral Babinski reflex were bilaterally irrelevant and the patient was transferred to the neurology service. The nasogastric probe was

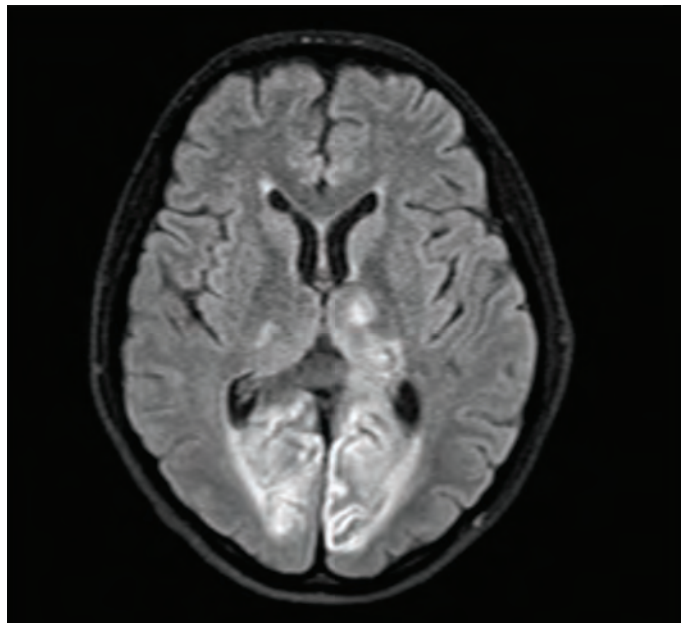

Figure 1. Cranial diffusion MR: diffusion restriction in favor of symmetrical acute infarction in pariyetooxypital, occipital lobe, temporal lobe medial. In both thalamus, areas showing diffusion restriction in favor of acute infarction in the right half of the pons
MR: Magnetic resonance

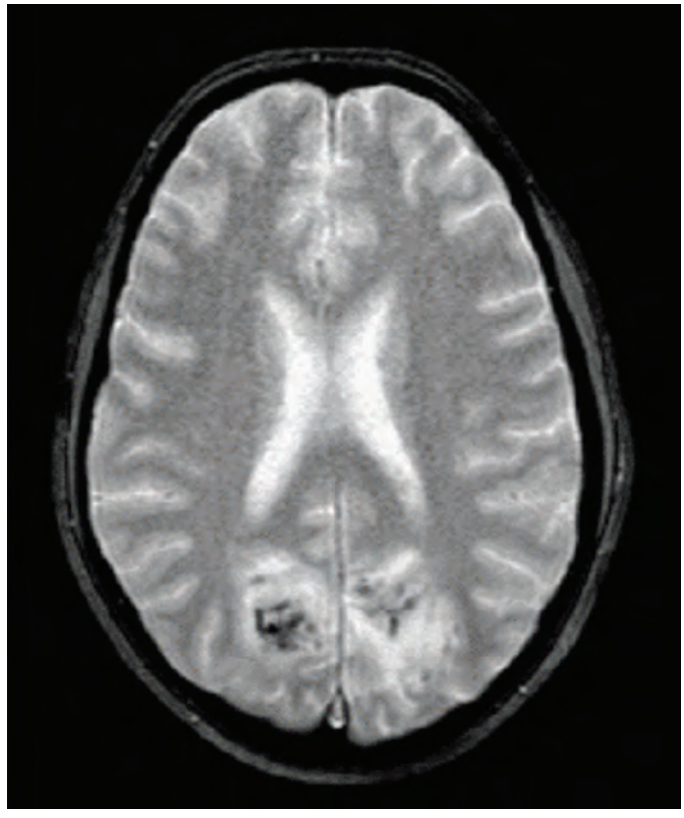

Figure 2. Cranial CT: Large hypodense areas in pons, both cerebral hemispheres, bilateral occipital lobe, temporal lobe, thalamus. Both cerebral hemispheres are edematous. Third ventricle has a semicompressed appearance
CT: Computed tomography

inserted because of decreased gag reflex (gag) and inability to swallow during Neurology service follow-up. The patient continued to practice daily physical therapy exercises and was discharged with recommendations.

DISCUSSION

Thalamic infarction may be unilateral or bilateral. Bilateral paramedian infarction has a classical triad characterized by impaired consciousness, memory dysfunction, vertical gaze paralysis, and neuropsychiatric disorder. Sensory disorders are observed in Bilateral thalamogeniculate artery infarction (5). Occlusion of the Percheron artery, usually caused by bilateral paramedian thalamus entrenched infarction in conjunction with the upper section of the mesencephalon, is extremely rare and has been reported in about 0.1-2% of all ischemic stroke cases (6,7). Percheron artery occlusion is a condition that causes bilateral thalamic lesion. Other conditions that may cause this include top of the basilar artery syndrome and deep cerebral vein thrombosis. Top of the basilar artery syndrome can be presented with bilateral thalamic infarction, but it can also be accompanied by infarction in the irrigation areas of the superior cerebellar artery and posterior cerebral artery. BTIs, which can also be seen as part of the top of the basilar artery syndrome, can rarely develop isolated (8). In the etiology of BTI, it is often (2/3) atherosclerotic small vascular disease, followed by artery-to-artery embolism and cardioembolism (9). Atherosclerosis most commonly affects the first few cm of the basilar artery. The majority of patients have chronic diseases such as hypertension and diabetes mellitus that can cause minor vascular disease (10). Stroke risk increases in pregnancy, is highest in the third trimester and postpartum period (11). Associated mortality is 8% to 15%, and hypercoagulopathy during pregnancy is thought to play a causal role. The direct role of caesarean section operation is unclear, but neurological findings that may occur due to hemodynamic instability, especially observed under spinal anesthesia, should be carefully evaluated. Examples in the literature for reasons such as rare occurrence of this complication, misdiagnosis, proper retention of data or failure to report cases are in the minority. First, Watanabe et al. (12) reported a case of cortical blindness due to transient ischemic neurological deficity after cesarean operation under spinal anesthesia in 1997. Second, Mathur et al. (13) also reported a case of pitoutier apoplexy which developed due to transient cerebral vasoconstriction syndrome after cesarean operation under spinal anesthesia in 2014. In patients with acute thalamic infarction, a non-contrast CT should be taken first to rule out bleeding (14).

CONCLUSION

In order to prevent misdiagnosis and discharge, it is useful to perform MRI on the diagnosis of BTI, especially in young patients with no history of underlying chronic disease. BTI is a diagnosis that should be kept in mind in the differential diagnosis of neuropsychiatric diseases by emergency department physicians, especially in patients with acute onset complaints. In general, the prognoses of thalamic infarctions are positive in terms of mortality and persistent neurological deficit.

Ethics:

Informed Consent: Consent was obtained from patients for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A., İ.A., A.C.Ö., K.Y., O.A., N.T., Concept: N.A., İ.A., A.C.Ö., K.Y., N.T., Design: N.A., A.C.Ö., N.T., Data Collection or Processing: N.A., İ.A.,A.C.Ö., K.Y., Analysis or Interpretation: N.A., N.T., Literature Search: N.A., İ.A., A.C.Ö., K.Y., O.A., Writing: N.A., N.T.

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