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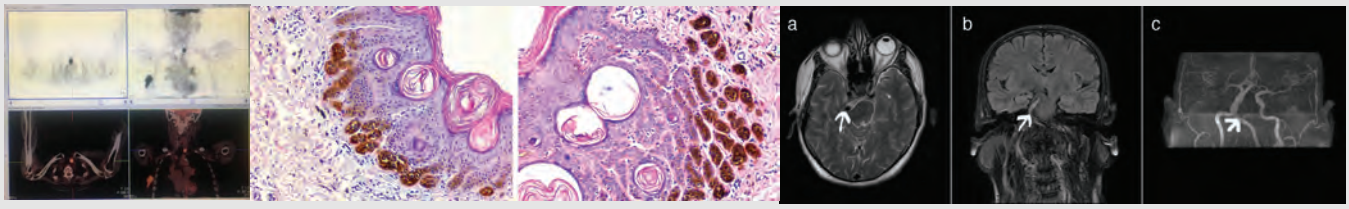

Highlights

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- Name(s), affiliations, highest academic degree(s), e-mail addresses, and ORCID IDs of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: 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).

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, 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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Units should be prepared in accordance with the International System of Units (SI).

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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.

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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).

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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).

Table 1. Limitations for each manuscript type

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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CONTENTS

REVIEW

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New Developments in Oncological Treatment: Targeted Treatments and Immunotherapy

Funda Yılmaz, Berna Öksüzoğlu

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Abstract

In the last 20 years, when we started to understand cancer biology better, targeted therapies and immunotherapies have been developed in systemic treatments and they have started to take their place as monotherapy or combined therapies in routine practice. Treatments that affect specific molecules are called targeted therapies. Monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TKIs) and those affecting the proliferation cascade constitute the majority of targeted therapies currently used. mAbs are targeted molecules produced from a single B-cell clone by antigen exposure. Most immunotherapeutics currently in use are in the form of mAbs. The targets of mAbs that we frequently use in cancer treatment today are human epidermal growth factor receptor-2 (HER-2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor, nuclear factor kappa-B ligand receptor activator, programmed death-1 and programmed death ligand-1. Treatments for tyrosine kinases, which play an important role in growth signal modulation, are used in many types of cancer. TKIs are small molecules and are used orally. The most commonly used TKIs are anti-angiogenic multikinase inhibitors. However by the EGFR and anaplastic lymphoma kinase inhibitors, a great progress has been made especially in the treatment of non-small cell lung cancer. Again BRAF/MEK, smoothened/hedgehog pathway, poly (ADP-ribose) polymerase, phosphoinositide 3-kinase, HER-2 inhibitors are other TKIs in use. The mammalian target of rapamycin pathway is also used as a target in many cancers. Immunotherapies are therapies that regulate the immune microenvironment, strengthening the immune system and allowing immune cells to fight against tumor cells. The effect of immunotherapy on cancer cells has been demonstrated by the high dose interferon, which was the first immunotherapy used. It consists of cancer vaccine, oncolytic viruses, *ex vivo* activated T-cell and natural killer cell transfer and immune checkpoint inhibitors. All these treatments contribute significantly to the survival and quality of life of patients with more antitumor efficacy. A large number of new molecules are being researched going forward, and promising advances in cancer treatment will continue.

Keywords: Cancer, targeted therapy, immunotherapy

INTRODUCTION

Traditional cancer treatment consists of surgery, radiotherapy and chemotherapy. While surgery and radiotherapy are mostly used in localized disease, systemic chemotherapy is mostly used as the primary treatment in metastatic disease. However, since conventional chemotherapeutic drugs mostly target rapidly growing cancer cells, they also cause many undesirable side effects by affecting fast growing normal tissues such as blood and gastrointestinal system cells. In the last two decades, targeted therapies that eliminate or inactivate cancer cells have been developed with a better understanding of cell chemistry and genome (1,2). Treatments that aim for a specific molecule and aim for more effect and less side effects are called targeted therapies. In this article, we tried to talk about target therapies and immunotherapies that have broken ground in oncology in recent years.

Targeted agents in oncology can be classified as: Monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TKI), those affecting

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the proliferation cascade, and others. In Table 1, we tried to summarize some of the targeted drugs and immunotherapy options detailed in this article and that can be used in most of our country.

TARGETED TREATMENTS

1- Monoclonal Antibodies

Antibodies are molecules formed by antigen exposure by B lymphocytes. Antibodies produced by the normal immune system are polyclonal and are produced from many B lymphocyte clones. On the other hand, mAbs used for targeted treatments are commonly produced from a single clone.

mAb types are classified according to their source. When naming murine mAbs, they take the "-omab" suffix and are the most immunogenic. When naming chimeric mabs, they take the suffix "-xmab", the humanized ones the "-zumab" suffix, and the "-umab" suffix while naming the completely human-sourced mabs (at least immunogenic) (3).

The target of the most commonly used mAbs in routine practice in oncology is human epidermal growth factor receptor-2 (HER-2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), nuclear factor kappa-B ligand receptor activator, and programmed death-1 (PD-1), which will be discussed under the immunotherapy title and programmed death ligand-1 (PDL-1) (3).

a- Anti-HER-2 monoclonal antibodies

The first use of modern mAb therapy in solid tumors was achieved with the HER-2 mAb trastuzumab (3). Trastuzumab exerts its antitumoral effect by binding to the extracellular domain of the HER-2 receptor, preventing cell-mediated cytotoxicity and ligand-independent HER-2 receptor dimerization (4,5). It is used in HER-2-expressing breast, stomach, and gastroesophageal junction cancers and the most important dose-limiting side effect is cardiotoxicity (6). Pertuzumab binds to HER-2 domain-2, preventing HER-2/HER3 dimerization. The region where trastuzumab and pertuzumab are bound is different from each other and their target properties provide a complementary mechanism for targeted therapy (7). Ado-trastuzumab emtansine is an antibody-drug conjugate that is a microtubule inhibitor fungal toxin emtansine in combination with trastuzumab (4,8,9).

Table 1. Targeted drugs and immunotherapy options

Target therapies		
Monoclonal antibodies	Trastuzumab	Panitumumab
	Ado-trastuzumab emtansin	Bevacizumab
	Pertuzumab	Ramucirumab
	Cetuksimab	-
Tyrosine kinase inhibitors	Sorafenib	Afatinib
	Sunitinib	Osimertinib
	Pazopanib	Crizotinib
	Regorafenib	Ceritinib
	Axitinib	Alektinib
	Erlotinib	Lorlatinib
	Gefitinib	Imatinib
Affecting the proliferation cascade and others	Palbociclib	Olaparib
	Ribociclib	Talazoparib
	Dabrafenib - trametinib	-
	Everolimus	-
Immunotherapies		
Immune chekpoint inhibitors	Pembrolizumab	Durvalumab
	Nivolumab	Avelumab
	Atezolizumab	Ipilimumab
Others	Interferon alpha-2b	CAR-T cell theraphy
	Cancer vaccines	-
	Oncolytic vaccines	-

CARR-T: Chimeric antigen receptor

This molecule has three properties: The anti-HER-2 function of trastuzumab combined with emtansine-induced tissue-specific expression and cytotoxicity (4,10). Margetuximab is an anti-HER-2 antibody that binds with high affinity to both low and high affinity forms of CD16A, an important Fc receptor for antibody-dependent cell-mediated cytotoxicity against tumor cells (11). Trastuzumab deruxtecan (DS-8201), a powerful topoisomerase inhibitor developed in recent years, is a humanized mAbs conjugate with the same amino acid sequence as trastuzumab specifically targeting HER-2. Its efficacy has been demonstrated in metastatic breast cancer patients who have previously received multiple lines of anti-HER-2 therapy (12).

b- Anti-EGFR monoclonal antibodies

Clarifying the biological basis of metastatic colorectal cancer has played an important role in the development of multi-targeted therapies for EGFR and mitogen activated protein kinase (MAPK) pathways, which play an important role in disease progression. In this context, anti-EGFR mAbs, cetuximab and panitumumab, are important therapeutics that block the activation of the MAPK pathway by targeting the extracellular domain of EGFR (13). The efficacy of panitumumab has been demonstrated in the ras-wild type metastatic colorectal cancers, and and cetuximab in ras-wild type metastatic colorectal cancer, head and neck cancers and non-small cell lung cancers. (14). Acneiform skin eruptions are common with anti-EGFR treatments, and dose reduction may be required in case of severe rash (6).

c- Anti-VEGF monoclonal antibodies

VEGF is the most important angiogenic growth factor. The growth of primary and metastatic solid tumors requires robust vascularity, so the VEGF signaling pathway has been an important pathway for chemotherapy. Bevacizumab is a recombinant humanized mAb targeting all forms of VEGF (14). It is indicated in colorectal cancer, non-squamous non-small cell lung cancers, ovarian, cervical and fallopian tube cancers, and primary peritoneal carcinoma (6). Ramucirumab is an IgG1 antibody that targets VEGF-R2. VEGF-A inhibits binding to VEGF-C and VEGF-D and ramicurumab is used in the treatments of advanced gastric and gasroesophageal junction adenocarcinomas, metastatic non-small cell lung cancers and metastatic colorectal cancer (14). Aflibercept is a recombinant fusion protein containing extracellular parts of human VEGF-R1 and 2. It binds to VEGF-A, VEGF-B and placental growth factor. In combination with FOLFIRI treatment, its benefit has been shown in patients with colorectal cancer (15). Besides the common side effects of anti-VEGF treatments such as hypertension and proteinuria, the dose-limiting side effects are thromboembolism, gastrointestinal perforations and bleeding (6).

2- Tyrosine Kinase Inhibitors

Kinases are also called phosphorylases. These transfer a phosphate group from a high energy donor molecule such as ATP to a specific substrate. Protein kinase phosphorylated proteins make functional changes in the target protein (16). Tyrosine kinases play a critical role in the modulation of growth factor signals. Active forms of these enzymes can cause an increase in tumor cell proliferation and growth, an antiapoptotic effect, and promote angiogenesis and metastasis. In addition to growth factors activation, protein kinase activation via somatic mutation is a common mechanism of tumorigenesis. Since all these effects are initiated by receptor tyrosine kinase activation, its inhibitors play a key role in target therapies (2).

TKIs are small molecules and, unlike mAbs, they can easily enter the cell (16,17).

While mAbs can only act on molecules expressed or secreted on the cell surface, small molecule TKIs are largely hydrophobic and can easily enter cells where the receptors can easily interact with intracellular domains and intracellular signaling molecules. As a result, small molecule TKIs can block the activation of various signaling pathways intracellularly (16). Due to the structure of ATP-binding pockets in protein kinases, small molecule agents show high affinity for many members of the receptor tyrosine kinase family, including PDGFR, Raf, EGFR and other targets (15). The multikinase inhibitor profile of some small molecule inhibitors offers the possibility of disrupting several independent biological pathways vital for tumor proliferation and metastasis (18,19).

a- Anti-angiogenic receptor tyrosine kinase inhibitors

In physiological conditions, angiogenesis is under a relatively dynamic homeostasis tightly controlled by pro-angiogenic and anti-angiogenic regulators. In cancer, however, the pro- and anti-angiogenic balance is disturbed and leads to the transition to angiogenesis (20,21). Tumor angiogenesis is a complex mechanism regulated by multiple signaling pathways (20).

Many multi-targeted anti-angiogenic agents have been developed that inhibit multiple signaling pathways (20,22). Sorafenib is a multikinase inhibitor indicated in advanced stage renal cell carcinoma, hepatocellular carcinoma and metastatic differentiated thyroid cancer. Sorafenib targets VEGFR-2, EGFR-3, PDGFRβ, FLT-3, c-kit, RET and RAF. (23-25).

Sunitinib is a multikinase inhibitor similar to sorafenib, but with different specific targets, PDGFRα, PDGFRβ, VEGFR-2 and 3 and c-KIT. It is indicated in the treatment of advanced stage renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors (14).

Pazopanib is an effective multikinase inhibitor against VEGFR-1, 2 and 3, PDGFRα and β, c-KIT receptors (20,26). It is indicated in advanced stage renal cell carcinoma and soft tissue sarcomas that have previously received chemotherapy (8).

Lenvatinib inhibits VEGFR-1, 2 and 3, FGFR-1, 2, 3 and 4, PDGFRα, RET and c-KIT (23,27,28). Lenvatinib is indicated in radioactive iodine refractory differentiated thyroid cancer, advanced stage renal cell carcinoma, and unresectable hepatocellular carcinoma (23,29).

Regorafenib inhibits VEGFR-1, 2 and 3, PDGFRα and β, FGFR-1 and 2, Tie2 and c-KIT receptors (20,30). It is indicated in metastatic colorectal cancer that progressed after standard therapy and in gastrointestinal stromal tumors progressed with imatinib and sunitinib (6).

Cabozantinib is an inhibitor of VEGFR-1, 2, 3, MET, RET, KIT tyrosine kinase and is used in metastatic renal cell carcinoma and medullary thyroid cancer (6). Axitinib VEGFR-1, 2 and 3 targets the PDGFRα and β, c-KIT receptor and is indicated in the second-line treatment of renal cell carcinoma (20,31).

b- EGFR tyrosine kinase inhibitors

Activating EGFR mutations are seen in 15-20% of non-small cell lung adenocarcinomas, and the most common of these mutations are exon 19 deletion and exon 21L858R mutation (32,33). Activating EGFR mutations (except exon 20 insertion) are sensitive to first generation EGFR TKIs (32). Erlotinib and gefitinib, first-generation EGFR TKIs, bind competitively and reversibly to the ATP binding site of EGFR tyrosine kinase. However, after an average of 12 months of response, resistance develops in all patients, including in approximately 50% of the patients with EGFR T790M resitance mutations. Therefore, the 2nd generation EGFR TKIs afatinib, dacomitinib and neratinib were developed not only for the T790M mutation, but also for EGFR activating mutations and wild type EGFR. However, although these agents have been shown to be effective in the T790M mutation *in vitro*, their clinical effects have remained weak (34). Unlike second generation EGFR tyrosine kinases, third generation EGFR TKIs act more specifically and irreversibly against T790M and activating EGFR mutations. Osimertinib is the first to be approved among the third generation EGFR TKIs (34). The most common side effects of EGFR TKIs are rash and diarrhea (14).

c- ALK tyrosine kinase inhibitors

About 85% of lung cancers are non-small cell in histology and only 5-7% of nonsmall cell carcinoma are anaplastic lymphoma kinase (ALK) mutation and approximately 1% *ROS1* gene rearrengement. (35). Crizotinib, a first generation ALK tyrosine kinase inhibitor that binds competitively to the ATP binding site, has been approved in locally advanced and metastatic ALK mutant non-small cell cancers (36).

Due to acquired resistance to crizotinib, the activity of this tyrosine kinase is limited. Secondary mutations in the *ALK* gene are thought to be the most common mechanisms mediating resistance to ALK inhibitors such as crizotinib (36).

Ceritinib, alectinib and brigatinib, which are second generation ALK TKIs developed to overcome crizotinib resistance, are also effective in first-line therapy (35,36). Alectinib treatment has more efficacy with less side effects compared to crizotinib in naive patients (35,37). Lorlatinib, entrectinib and ensartinib are third generation ALK inhibitors developed to overcome second generation inhibitory resistance in ALK positive lung cancer patients (36). Lorlatinib crosses the blood-brain barrier and reaches high intracranial concentrations (38). In patients with previously untreated advanced ALK-positive NSCLC, lorlatinib has a significantly longer progression-free survival and a higher frequency of intracranial response than crizotinib. The incidence of grade 3 or 4 adverse events was higher with lorlatinib than with crizotinib, due to varying lipid levels (39).

d- Anti-HER-2 tyrosine kinase inhibitor

Lapatinib is EGFR (ErbB1) and HER-2 (ErbB2) related small molecule tyrosine kinase and inhibits the downstream signal. This agent is used in combination with oral fluoropyrimidine capecitabine in HER-2 positive metastatic breast cancer who have previously received anthracycline, taxane, and trastuzumab (14). The most common side effect is diarrhea (6).

3- Affecting the Proliferation Cascade and Others

a- Cyclin-dependent kinases (CDK)4/6 inhibitors

Cell cycle abnormalities are common in cancer and have long been a potential treatment target. CDK are critical regulatory enzymes that direct cell cycle transitions and cell division (40,41-44). In recent years, small molecule inhibitors targeting this mitogenic pathway have been developed (45). Among the CDK4/6 inhibitors, palbociclib, ribociclib and abemaciclib are indicated in combination with hormonotherapy (tamoxifen, aromatase inhibitor, and fulvestrant) in metastatic in metastatic hormone

receptor positive HER-2 negative breast cancer (40). Despite similar mechanisms of action, the dose-limiting side effects of these agents are different. Neutropenia, diarrhea and fatigue are dose-limiting for palbociclib, while neutropenia, mucositis, asymptomatic thrombocytopenia, pulmonary embolism, creatinine increase, hyponatremia, and QTc prolongation are dose-limiting side effects for ribociclib (45-47).

b- BRAF/MEK inhibitors

The MAPK cascade is an intracellular signaling pathway involved in the regulation of cellular proliferation and the survival of tumor cells. Several different mutations involving BRAF or NRAS activate the MAPK pathway and cause an increase in cellular proliferation by making an oncogenic effect (48). The activating *BRAF* gene mutation is seen in approximately 50% of melanomas. V600E mutation is seen in more than 70% of BRAF mutations and V600K mutation is seen in 10-30% (49). Inhibition of the MAPK pathway with the combined use of BRAF and MEK inhibitors has been an effective treatment option in the treatment of BRAF mutant melanoma (50). Trametinib is the first MEK inhibitor approved for the treatment of BRAF mutated metastatic melanoma that has not been previously treated with BRAF inhibitors, and is approved in combination with the BRAF inhibitor dabrafenib. In addition, cobimetinib in combination with another BRAF inhibitor vemurafenib is another MEK inhibitor approved for the treatment of BRAF mutated metastatic melanoma. The MEK inhibitor binimetinib in combination with the BRAF inhibitor encorafenib is under clinical development (48).

c- Phosphoinositide 3-kinase (PI3K) inhibitors

The PI3K/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway plays an important role in cell proliferation, cell life and angiogenesis. PI3K mutations are often seen in estrogen receptor (ER) positive breast cancer. Specifically, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutations encoding the alpha isoform of the catalytic subunit of PI3K are detected in more than 40% of ER-positive breast cancer (51). Previous studies evaluating fulvestrant in combination with pan-isoform PI3K inhibitors (buparlisib and pictilisib) or beta isoform protector taselisib have shown limited improvements in progression-free survival in patients with endocrine-resistant disease, but due to their toxicity (gastrointestinal side effects, transamin increase and hyperglycemia) their therapeutic usage is limited (52-56). The effectiveness of alpha isoform-specific PI3K inhibitor alpelisib, independent of the previous use of CDK4/6 inhibitors, in combination with fulvestrant in hormone receptor positive HER-2 negative and PI3K mutant breast cancer patients was shown in the SOLAR-1 study, and the efficacy after the use of CDK 4/6 inhibitors by its anticipated side effects was shown in the BYLieve study (51).

d- Mammalian target of rapamycin inhibitors

mTOR is an intracellular protein that has a central role in cellular function. It acts as a nutrient sensor and mediates downstream of receptor tyrosine kinases that control cell growth, protein synthesis, autophagy, and angiogenesis (57). Dysregulation of the mTOR pathway is associated with cancer and other diseases (58). Everolimus, one of the mTOR inhibitors, is used in combination with exemestane in hormone receptor positive, HER-2 negative breast cancer, and used as monotherapy in gastrointestinal neuroendocrine tumors, renal cell carcinoma, renal angiomyolipoma and tuberous sclerosis complex. Temsirolimus is indicated in the treatment of advanced stage renal cell carcinoma (6).

e- Smoothened (SMO)/hedgehog inhibitors

Advanced basal cell carcinoma (BCC) constitutes a small proportion of BCCs and is not suitable for standard treatments due to low efficacy, high risk of recurrence and excessive morbidity. The impact of the sonic hedgehog (Shh) pathway in the development of BCC has led to the development of systemic Shh pathway inhibitors that contribute to new treatment options and survival in patients with advanced BCC (59).

Vismodegib and sonidegib, used in BCC treatment, show their activity by binding and inhibiting SMO, which is a transmembrane protein in the hedgehog pathway (6).

f- Poly (ADP-ribose) polymerase (PARP) inhibitors

Heterozygous germline mutations in the *BRCA1* and *BRCA2* genes result in a high risk of breast cancer (up to 85% lifetime risk), ovarian cancer (10% to 40%) and a significantly increased risk of pancreatic, prostate, and male breast cancer (60). PARP enzymes are involved in normal cell homeostasis such as DNA transcription, DNA repair, and cell cycle (6). BRCA1 and BRCA2 mutation tumors are sensitive to PARP inhibitors because they have a specific DNA repair defect (61). It has been suggested that PARP1/2 expression levels may be the biomarker for the inhibitory response. While olaparib and veliparib are highly selective inhibitors of PARP1 and PARP2; niraparib, rucaparib and talazoparib are general PARP inhibitors (54). PARP inhibitors can cause various cytopenias. While olaparib, rucaparib and talazoparib can cause severe anemia, niraparib can cause thrombocytopenia more frequently besides anemia (62).

IMMUNOTHERAPY

Immunotherapies are therapies that strengthen the immune system by regulating the immune microenvironment, thereby allowing immune cells to be protected from attacking tumor cells (63). Compared to conventional cancer treatments, cancer immunotherapy contributes significantly to life expectancy and quality of life. Immunotherapy has proven itself in many types of cancer, from the metastatic stage palliative to (neo) adjuvant therapy, by the molecules and clinical studies developed in the last 10-15 years (63). Immunotherapies in cancer treatment were highlighted as "publication of the year" in Science magazine in 2013 and "progress of the year" in 2015 by the American Society of Clinical Oncology (64-66). Immunotherapy strategies consist of antibodies or recombinant proteins that co-stimulate or block cells, named as cancer vaccine, oncolytic viruses, *ex vivo* activated T-cell and natural killer (NK) cell transfer, and immune checkpoint inhibitors (67).

Interleukin-2, the first immunotherapy used in human cancers, is a T-cell growth factor (68). Although its use after immune checkpoint inhibitors decreased significantly, high-dose bolus IL-2 provided a long-term response rate in a small proportion of patients with melanoma and renal cell carcinoma, and showed that the immune system could destroy cancer cells (69).

Aldesleukin is a human recombinant IL-2 analogue. The most important side effect of IL-2 therapy is that it causes capillary escape syndrome, causing fluid leakage into visceral organs and dysfunction (68).

a- Interferon Alpha-2b

Interferon alpha-2b activates certain enzymes by binding to the specific membrane receptor on the cell surface and exerts immunomodulatory effects such as suppressing cell proliferation, increasing phagocytic activation of macrophages, increasing cytotoxic effect of lymphocytes to target cells, and decreasing virus replication in virus-infected cells. Long-acting pegylated versions of interferon are effective in melanoma, kaposi sarcoma, follicular lymphoma and hairy cell leukemia (6).

b- Cancer Vaccines

Cancer vaccines has antitumor activity by providing specific stimulation of the immune system using tumor antigens. Different vaccine strategies have been developed (70). Compared to standard cancer treatments, tumor vaccines theoretically have many advantages. It is possible to create specific cancer therapy with vaccine therapy. Long-lasting anti-tumor responses can be achieved by stimulating tumor-specific memory T-lymphocytes. The incidence of side effects of cancer vaccines in individuals is rare. Among these side effects; transient fever, flu-like symptoms or autoimmune reactions are included (71). Cancer vaccines include antigen vaccines, anti-idiotype vaccines, dendritic cell vaccines, genetic vaccines and tumor cell vaccines (71).

Currently the only vaccine-based therapy approved for cancer treatment is sipuleucel-T. Sipuleucel-T is a vaccine treatment produced by autologous dendritic cell engineering targeting prostatic acid phosphatase used in castration resistant prostate cancer (72). It is obtained by culturing the peripheral blood antigen presenting cells (monocytes and lymphocytes) taken from the patient by plasmapheresis with prostate cancer cell protein PAP and granulocyte-macrophage colony-stimulating factor. It is injected back to the patient after purification (73).

c- Oncolytic Viruses

Oncolytic viruses mediate antitumor effects in a variety of ways. Viruses can infect cancer cells to stimulate the presentation of tumor-associated antigens, stimulate a "distress signal" to the less immunolerant tumor microenvironment, and serve as transduction tools for the expression of immune modulatory cytokines (74).

Talimogene laherparepvec is a live attenuated herpes simplex type 1 virus, genetically modified, developed to provide antitumor response in tumor cells through selective viral replication and stimulation of antitumor immunity. It is the first oncolytic virus approved for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in malignant melanoma recurring after the first surgery (75).

d- Chimeric Antigen Receptor (CAR) T Cell Therapy

CAR-T cell therapy provides a great advantage in personalized cancer treatment, in which the patient's own T-cells are genetically modified to produce synthetic receptors that bind to the tumor antigen. CAR-T cells are then infused into the patient to attack and destroy chemotherapy resistant cancer. CAR-T cell therapy has dramatic response and complete remission rates in B-cell hematologic malignancies. CAR-T cell therapy is one of the first successful examples of synthetic biology and personalized cellular cancer therapy (76).

e- Immune Checkpoint Inhibitors

Immune checkpoints are located on the surface of T-cells or tumor cells as effective targets to inhibit the overactivation of T-cells. Under normal conditions, immune control proteins are intended to prevent autoimmune disease damage by suppressing the excessive immune response, but when the tumor develops,

they inhibit the recognition of the tumor cell by T-cells and weaken the immune system's ability to recognize and destroy tumor cells (77).

Cytotoxic T lymphocyte antigen (CTLA-4) acts on the surface of CD4 and CD8 T lymphocytes by binding to the co-stimulatory receptors CD80 and CD86 (B7-1 and B7-2) on the antigen-presenting cell surface with a higher affinity than the T-cell co-stimulator (78).

The interaction of CTLA-4 with these ligands inhibits the T-cell response by showing a braking effect (79). Ipilimumab, one of the anti-CTLA-4 antibodies, is an immune checkpoint inhibitor of which first clinical studies have been published and its contribution to survival in metastatic melanoma has been proven (80). PD-1 is a transmembrane protein expressed on the surface of T-cells, B-cells, and NK cells.

PD-1 binds to ligand 1 and 2 (PDL-1 and PDL-2) and acts as an inhibitor. The interaction of PD-1 with PDL-1/2 directly inhibits tumor cell apoptosis, promotes peripheral T effector cell depletion and supports the transformation of T effector cells into Treg cells (81,82). PD-1/PD-L1 mAbs are used in melanoma, non-small cell lung cancers, head and neck cancers, Hodgkin's lymphoma, urinary epithelial cancer, gastric cancer, kidney cancer, liver cancer and many other cancers. Because these antibodies are more selective, they have fewer side effects and are more reliable than CTLA-4 inhibitors (77,83-87). PD-1 mAbs are pembrolizumab, nivolumab, cemiplimab, toripalimab, and sintilimab. PDL-1 mAbs are atezolizumab, avelumab, durvalumab and pidilizumab (77).

Immunotherapy combinations such as ipilimumab and nivolumab are associated with increased toxicity in melanoma studies, despite a greater response rate (68). Immune checkpoint inhibitors can cause a large number of non-specific T-cell activation-related and general immunological side effects. Many autoimmune events can occur, but rheumatological tests are usually negative. Mostly the skin, gastrointestinal system, liver, endocrine organs and lungs are affected, but immune-related side effects may develop in all organs and the main treatment is corticosteroids (68). The response pattern to immune checkpoint inhibitors may differ from the response to conventional chemotherapy or molecular targeted therapies (88). Patients may develop a temporary worsening of the disease, which occurs with the progression of known lesions or the emergence of new lesions before the disease is stabilized or the tumor regresses, and this phenomenon, which we call pseudoprogression, may be confused with real progression. However, these delayed responses are not usually observed in patients with symptomatic worsening, so continued treatment is not recommended in patients with symptomatic worsening (89). For all these reasons, instead of response evaluation criteria in solid tumors (RECIST) used for conventional therapies, a revised response and evaluation criteria was described for immune check point inhibitors, namely immune related response criteria (iRECIST)(68).

CONCLUSION

With a better understanding of the molecular biology and genetics of cancer, serious developments have been made in cancer treatment especially in recent years. Numerous new targeted molecules and immunotherapy approaches have been found to provide higher antitumor effect with fewer side effects, and they have started to enter our clinical practice. With targeted therapies and immunotherapies, there is a significant increase in the life expectancy of patients. Studies on drugs and immunotherapies that target many new molecules are still ongoing, and today we are fighting cancer with weapons much more powerful than conventional therapies. Recent advances in cancer treatment promise even greater hope for the future.

Ethics

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Authorship Contributions

Surgical and Medical Practices: F.Y., B.Ö., Concept: F.Y., B.Ö., Design: F.Y., B.Ö., Data Collection or Processing: F.Y., B.Ö., Analysis or Interpretation: F.Y., B.Ö., Literature Search: F.Y., B.Ö., Writing: F.Y., B.Ö.

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Short-term Efficacy of Dienogest in Improving Pain in Patients with Endometriosis: A Single-center Experience

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Abstract

Objective: Endometriosis is a common disease that affects 5%-15% of women of reproductive age. This study aimed to evaluate the effect of dienogest (DNG) on improving pain scores of patients with endometriosis.

Methods: Data of 77 women who were admitted to the endometriosis clinic from March 1, 2015, to March 1, 2017, were evaluated. Patients were divided into 2 groups: DNG group (n=46) or group that denied use of any medication (expectant management group, n=31). The main presenting symptoms were graded using the visual analog scale (VAS). Age, parity, gravidity, body mass index (BMI), VAS scores, and further surgery requirement of the study groups were compared.

Results: The most common presenting symptom was dysmenorrhea (79.2%), and the least common was dysuria (7.8%). No statistically significant difference was found between the study groups in terms of age, parity, gravidity, BMI, and further surgery requirement. A significant difference was found in the reduction of dysmenorrhea, dyspareunia, dyschezia, and pelvic pain VAS scores between the study groups, and more reduction was observed in the DNG group after 6 months of follow-up ($p<0.001$, $p=0.04$, $p=0.009$, and $p=0.01$, respectively).

Conclusion: DNG might be an alternative treatment for reducing pain symptoms related to endometriosis.

Keywords: Dienogest, endometriosis, pelvic pain, treatment outcome

INTRODUCTION

Endometriosis is an abnormal growth of endometrial tissue other than the inner uterine layer and affects approximately 10% of women of reproductive age. It is also observed in 70% of women with lower abdominal quadrant pain and 48% of patients with infertily (1,2). In addition, it could cause severe dysmenorrhea, dysuria, dyspareunia, and even dyschezia (2). Till date, medical therapy has been widely recommended for pain relief and suppression of endometriotic lesions (3).

Combined oral contraceptives (COC) are well tolerated with their minimal metabolic effects and are commonly used to suppress ovulation and reduce menstrual blood flow in women with endometriosis (4). In addition, gonadotropin-releasing hormone analogs (GnRH-a) evoke pharmacological menopause by suppressing ovulation and reducing ovarian steroidogenesis. However, its extended use is restricted due to the risk of decreased bone mineral density (BMD) (5).

To treat endometriosis-related symptoms, progestins are prescribed owing to their effects of inhibiting ovulation, reducing serum levels of estrogen resulting in endometrial atrophy, and decreasing levels of peritoneal inflammatory markers (6). Although progestins, such as desogestrel and medroxyprogesterone acetate, might cause several androgen-related side effects, new-generation progestins, such as dienogest (DNG) which is a fourth-generation, well-tolerated, semisynthetic selective progestin that possess the pharmacological features of 19-nortestosterone, have greater specificity on binding to progesterone receptors (7) and offer a

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local effect on endometriotic lesions, with little androgenic, estrogenic, glucocorticoid, or mineralocorticoid activity (8,9). Previous studies have reported that DNG not only suppressed ovulation and exerted antiproliferative effect, but also inhibited cytokine secretion in the stroma of endometrial cells, which leads to a reduction of endometriosis-related pain (10).

This study aimed to assess the effect of DNG on endometriosis-related pain in comparison with expectant management.

METHODS

After ethical approval was obtained from our Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2017/126), analysis of prospectively collected data of 77 patients diagnosed with endometrioma, confirmed by either ultrasonography or laparoscopic surgery, was performed. Patients who were admitted to our endometriosis outpatient clinic within the time period from March 2015 to March 2017 were evaluated retrospectively.

Basic clinical data such as age, parity, gravidity, body mass index (BMI), and further surgery requirement were derived from the patients' files and computer-assisted hospital database. The exclusion criteria were as follows: Presence of malignancy, bowel disease, history of bowel surgery, history of pelvic inflammatory disease, presence of any autoimmune diseases, discontinuation of medical treatment, and use of any hormonal or antiinflammatory or immune-regulatory medications in the previous 3 months.

After application of the exclusion criteria, the patients were divided into 2 groups: A group of patients who received a dose of 2 mg/day of DNG beginning at the early follicular phase of menstruation (DNG group, n=46) and a group of patients who refused any medical treatment despite the presence of pain symptoms (expectant management group, n=31).

The main presenting symptoms were dysmenorrhea, dyspareunia, dysuria, dyschezia, and chronic pelvic pain, which were graded using a visual analog scale (VAS). All patients were asked to complete VAS questionnaire at the 1st month and at 6th month follow-up visit to analyze their pain severity. The questionnaire used an 11-point numerical rating scale: 0 indicates painless state and 10 indicates the worst pain that they had ever experienced.

The study groups were compared in terms of age, gravidity, parity, BMI, main presenting symptom, and further surgery requirement. BMI was calculated as the ratio of weight (kg) to the square of height (m^2). Pelvic pain was defined as non-cyclic pain lasting at least 6 months, appeared in various body parts, such as the pelvis and abdominal wall, and caused serious disability or led to medical care (11).

Statistical Analysis

Data analysis was executed with SPSS (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp., Armonk, NY). Data were presented as the mean ± standard deviation. A one-sample Kolmogorov-Smirnov test was performed to evaluate the distribution of variables. Student's t-test was used for the comparison of parametric variables, and the Mann-Whitney U test, chi-square test, and Fisher's exact test were used to compare non-parametric variables. Dependent non-parametric values were also analyzed using Wilcoxon rank test to evaluate pain scores observed before treatment and after the follow-periods in both study groups. For all calculations, a p value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 34±7.8 years in the expectant management group and 32±7.27 in the DNG group. The mean BMI was 24.46±3.74 in the expectant management group and 23.56±4.87 in the DNG group. No significant difference was found between the study groups with regard to age, parity, gravidity, BMI, and further surgery requirement. Basic clinical data of the patients are shown in Table 1. The most common presenting symptom was dysmenorrhea (79.2%). The remaining symptoms were chronic pelvic pain (37.7%), dyspareunia (31.2%), dyschezia (19.5%), and dysuria (7.8%). No significant difference was found between the study groups in terms of the main presenting symptoms on admission. A significant difference was noted between the study groups in terms of the reduction in dysmenorrhea, dyspareunia, dyschezia, and pelvic pain VAS scores, and more reduction was observed in the DNG group at the end of the 6-month follow-up period ($p<0.001$, $p=0.04$, $p=0.009$, and $p=0.01$, respectively) (Table 2). We also analyzed

Table 1. Basic characteristics of the study population

	Expectant management group (n=31) mean ± SD	Dienogest group (n=46) mean ± SD	p value
Age (years)	34±7.8	32±7.27	0.31
Gravidity	0.93±1.12	0.84±1.05	0.73
Parity	0.9±1.04	0.69±0.86	0.42
BMI (kg/m^2)	24.46±3.74	23.56±4.87	0.15
Surgery after treatment (n/%)	1 (3.2%)	7 (15.2%)	0.07

BMI: Body mass index, SD: Standard deviation

pain scores observed before treatment and after follow-up periods in each study group. Although no significant difference was found in the expectant management group for pain scores before treatment and after the follow-up, a significant decrease in dysmenorrhea, dyspareunia, dischezia, and chronic pelvic pain, was found in the DNG group ($p<0.001$, $p=0.003$, $p=0.008$, and $p=0.001$, respectively) (Table 3).

DISCUSSION

Considering the detrimental effect of endometriosis surgery, many clinicians support the idea that medical treatment might be empirical, before any surgical intervention, by using analgesic and antiinflammatory drugs as the first-line therapy (12). In addition, COC pills and progestins, such as medroxyprogesterone acetate or norethisterone, are used as medical treatment and are known as safe, well-tolerated, inexpensive, and effective long-term treatment of endometriosis (3,12). On the contrary, GnRH-a, levonorgestrel-releasing intrauterine system, or opioid analgesics should be considered for those women who are resistant to first-line therapies (13). However, GnRH-a regimens are associated with hypoestrogenism-related symptoms, such as vaginal atrophy and decreased BMD, that restrain its clinical use as a long-term therapy (5).

Table 2. Comparison of the first visit and second visit endometriosis-related VAS scores of the study population

	Expectant management group (n=31) mean ± SD	Dienogest group (n=46) mean ± SD	p value
1st visit dysmenorrhea	4.91±4.12	6.73±3.39	0.09
2nd visit dysmenorrhea	4.41±3.96	3.69±3.55	0.43
1st visit dyspareunia	1.16±2.68	2.15±3.08	0.14
2nd visit dyspareunia	1±2.63	1.37±2.27	0.27
1st visit dyschezia	0.71±1.95	1.78±3.35	0.17
2nd visit dyschezia	0.71±1.95	0.93±2.18	0.51
1st visit dysuria	0.60±2.20	0.81±2.20	0.21
2nd visit dysuria	0.45±1.39	0.45±1.39	0.24
1st visit pelvic pain	1.8±3.07	2.45±3.20	0.39
2nd visit pelvic pain	1.74±2.90	1.34±2.07	0.89
Reduction of dysmenorrhea	-0.48±1.20	-0.43±3.08	**<0.01**
Reduction of dyspareunia	-0.16±0.73	-0.78±1.61	**0.04**
Reduction of dyschesia	0	-0.84±2.07	**0.009**
Reduction of urinary symptom	0	-0.34±1.35	0.09
Reduction of pelvic pain	-0.06±0.35	-0.08±2.10	**0.01**

VAS: Visual analog scale, SD: Standard deviation

Table 3. Difference between endometriosis-related VAS scores for the DNG group at 1st visit and 2nd visit (6th month)

	1st visit (on admission)	2nd visit (6th month)	p value
Dysmenorrhea	6.73±3.39	3.69±3.55	**<0.001**
Dyspareunia	2.15±3.08	1.37±2.27	**0.003**
Dyschesia	1.78±3.35	0.93±2.18	**0.008**
Dysuria	0.80±2.20	0.45±1.39	0.06
Pelvic pain	2.45±3.20	1.34±2.07	**0.001**

VAS: Visual analog scale, DNG: Dienogest

In previous studies, DNG, a fourth-generation, semisynthetic selective progestin, had been compared with a GnRH agonist such as buserelin, triptorelin, and leuprolide acetate, in terms of providing relief to pelvic pain and other endometriosis-related symptoms (10,14-18). Considering overall side effects, all those studies revealed that DNG had comparable unintended results such as irregular vaginal bleeding, headache, breast tenderness, and weight gain.

A study compared DNG and 19-nortestosterone-derivative progestin norethindrone acetate (NETA) in women with endometriosis (19,20) and found a statistically significant difference in the reduction of mean dysmenorrhea score in favor of the DNG group, but both NETA and DNG presented similar pain relief in women with deep endometriotic lesions. However, no significant improvements were observed in the quality of life scores or sexual functions (21,22).

Two studies have evaluated the long-term use of DNG by up to 52-53 weeks (18) and reported that DNG clinically improved endometriosis-related symptoms with a decrease in VAS scores. In these studies, most patients experienced abnormal menstrual bleeding as a side effect (16,18). In a 24-week placebo-controlled, randomized, double-blind, phase 3 study by Lang et al. (23) the efficacy and safety of 2 mg/daily DNG intake was evaluated in 255 Chinese women using endometriosis-associated pelvic pain (EAPP) score and safety variables including adverse events, laboratory parameters, bleeding patterns, and BMD. They concluded that a mean reduction in the EAPP score was well tolerated with few adverse events in favor of DNG and DNG had no effect on BMD levels after 24 weeks of treatment. Overall, in our study, we evaluated 6-month results of our study population and compared them with previous literature (23). We observed significantly improved endometriosis-related symptom scores when compared with the controls. Considering the significant reduction in dysmenorrhea, dyspareunia, dyschezia, and pelvic pain scores in our study, DNG

might reduce the secretion of inflammatory cytokines or might reduce endometrial foci by ovulation suppression.

Study Limitations

As study limitations, we did not evaluate the side effects of DNG and its effect on endometrioma size. Our results should be supported by larger case series with longer follow-up periods.

CONCLUSION

In summary, 2 mg daily intake of DNG is effective in the management of endometriosis, and DNG should be considered an alternative in alleviating pain in patients with endometriosis.

Ethics

Ethics Committee Approval: Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2017/126).

Informed Consent: The written informed consent was obtained from all of the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.K., İ.A., H.C., Design: C.K., H.C., Data Collection or Processing: E.B., İ.A., Analysis or Interpretation: M.E., L.Y., Literature Search: C.K., E.B. Writing: C.K.

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Does Latent Strabismus Affect Stereoacuity?

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Abstract

Objective: The purpose of this study is to determine the effect of latent strabismus on stereoacuity.

Methods: Stereoacuities of normal individuals, ranging in age from 18 to 35 years, were measured using the TNO or Titmus tests. The study population was divided into 2 groups regarding the achievement of the accepted excellent stereoacuity threshold of 30 arcseconds (group A) or not (group B). The relationship between latent deviation angles and stereoacuity levels were evaluated.

Results: Latent deviation angles ranged from 0 to 35 prism diopters (PD). Both TNO (r=0.380 p=0.002) and Titmus (r=0.306 p=0.015) stereothresholds tended to increase as the latent deviation angles increased. Group A included 27 participants who had either exophoria (18) or orthophoria (9), and the mean deviation angle of this group was 3.07±3.26 PD. Group B included 36 participants, 28 of whom had exophoria, three had esophoria, and the remaining five had orthophoria. The mean angle of deviation in group B was 6.50±6.92 PD. This value was statistically higher than the mean deviation angle in group A (p=0.012). Though none of the esophoric participants achieved excellent stereoacuity, the distribution of the deviation types did not cause any difference between the groups (p=0.077). The mean age of group A was found to be higher than that of group B (p=0.006).

Conclusion: Latent deviation can mask true stereosensitivity potentials of subjects to some extent during the stereotesting procedure.

Keywords: Stereopsis, latent deviation, TNO test, Titmus test

INTRODUCTION

Stereopsis is defined as the relative ordering of visual objects in depth. The differences between the locations of matching features on the retinas are termed binocular disparities, and the ability to perceive depth from these disparities is stereopsis (1). A normal level of disparity arises from the viewing of fixation point by both eyes with several minutes of the arc of angle difference (2). However, disparity might increase in cases of a monocular blur, ocular misalignment, and aniseikonia (3,4). High-grade stereopsis requires bi-foveal fixation, precise motor control of eyes, and bilateral high-level visual acuities as prerequisites (2,3,5). However, subjects with unexpectedly low-level stereoacuities can be seen, despite orthotropia and normal bilateral vision. Several explanations might account for this condition. Disparity-selective V1 neurons in the striate cortex of these subjects may be incapable of perceiving minor disparities that result in fine stereopsis (1). The false-negativity related to the stereotests used might be another explanation since the stereoacuities obtained in stereograms using targets with and without detectable monocular contours might differ quite a great deal (4,6-8). Stereotests are applied while the eyes are in dissociated conditions, and the manifestation of latent deviations during the procedure might prevent fusion and, consequently, stereopsis. It has been shown that microtropic subjects with a horizontal deviation exceeding 4-5 prism diopters (PD) were least likely to demonstrate stereopsis (9-12). However, these microtropic subjects usually have central suppression, besides microtropia, which might cause weak stereopsis. The effect of an

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isolated deviation on stereopsis can be determined by studying subjects with only latent deviation and no other anomaly, such as amblyopia, anisometropia, and strabismus history. This study aims to investigate whether latent deviation amplitudes affect measured stereoacuity levels using both contour-based (Titmus) and random-dot (TNO) stereograms in normal subjects.

METHODS

This prospective study was conducted with participants recruited from the hospital staff and medical faculty students. Informed consent was obtained from all individual participants included in the study. The study was performed in accordance with the tenets of the Declaration of Helsinki with the approval of the Institutional Review Board. Ethics Committee of İzmir Katip Çelebi University (decision number: 56, date: 06.02.2019).

All participants had full eye examinations, including best-corrected visual acuities, biomicroscopic anterior segment, and fundus examinations. Spherical equivalents of refractive errors were recorded. Next, an alternate cover test was used to determine if any latent deviation for distant and near fixation was present. If there was a latent deviation, control of the deviation for distance and near fixation was evaluated. Subjects who had control of the deviation immediately after 10 seconds of monocular occlusion were included. Deviations were measured for near and distant fixations using the prism-cover test. The Worth-4-Dot (W4D) test was used to evaluate fusion.

The criteria for inclusion in the research are given below.

1- Normal visual acuity in both eyes (at least 20/20 Snellen),

2- No prior history of amblyopia or amblyopia treatment,

3- No prior history of intermittent or manifest strabismus,

4- Anisometropia less than -1.00 diopter myopia or astigmatism and <+0.50 hypermetropia,

5- Fusion for distance and close in the W4D test, and

6- Age 18-35 years of old.

Stereoacuities were measured using both contour (Titmus test; Stereo Optical Co, Chicago, IL, USA) and random-dot (TNO test; 15th edition, Lameris Ootech BV) stereograms. The Titmus test uses contoured stimuli with polaroid glasses to separate the stimuli presented to each eye. Clues are presented that allow the circle with the disparity to be identified as different under monocular viewing conditions. The TNO test uses random-dot stimuli with red-green glasses to separate the images presented to each eye. There are no monocular clues that enable the identification of the stereotarget. Only the near stereoacuity thresholds were evaluated.

All participants had stereoacuity measurements in the same examining room and illumination conditions. The time required for each test was recorded. If the measured stereoacuity was above 60 arcseconds, stereosensitivity was retested with the same tests in the same circumstances to confirm the result. The lowest measurement was recorded if the measurements were not the same. Participants were divided into 2 groups, regarding the achievement of the excellent stereoacuity level (30 arcseconds) (13). Group A included participants who achieved 30 arcseconds stereoacuity, and group B included the others.

Statistical Analyses

The correlations between stereoacuity levels and latent deviation angles were tested using Pearson's correlation analysis. Either independent samples t-test or Mann-Whitney U test was used to compare the continuous variables of group A and B after testing the equality of variances of the groups with the Levene's test. The categorical variables of the groups were compared using the Pearson chi-square test. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 63 individuals who met the criteria, 45 were female. The mean age was 27.04±5.32 years. Absolute values of latent deviation angles ranged from 0 to 35 PD, with an average of 5.03±5.86 PD. The stereosensitivity threshold values of the Titmus stereotest ranged from 40 to 160 arcseconds, and the stereosensitivity threshold values with the TNO test ranged from 15 to 480 arcseconds. The time required to perform the Titmus stereotest was 30-60 seconds. On the other hand, performing the TNO test required 3-5 minutes. Fifty-nine participants (92%) showed 60 arcseconds or better stereosensitivity level at least in one of the tests, and fifty-five (87%) participants showed this level in both tests.

The common feature of four participants who could not achieve normal stereosensitivity in both tests was that the near-deviation angles were higher than those in the distance. There was convergence insufficiency type exophoria in three participants, and the fourth participant had convergence excess type esophoria. In these four cases, the near-deviation angles were 6-12 PD higher than the distance angles. Similar convergence-divergence imbalances were observed in three of the four participants, who achieved normal level stereoacuity in

only the Titmus test. The fourth case in this subgroup had the highest deviation (35 PD) of the study group for both near and distance fixations. Another common feature of these cases was their variable stereosensitivity thresholds detected on retesting to confirm their abnormally high stereosensitivity thresholds.

There was a significant correlation between the Titmus and TNO tests (r=0.802, p<0.001). However, as the near-deviation angles increased, stereosensitivity thresholds also increased in both tests but reached statistical significance at different levels (TNO, p<0.01; Titmus, p<0.05) (Table 1). Twenty-seven participants who achieved the perfect stereosensitivity level were grouped in group A, and the rest of the participants who had lower stereosensitivity were grouped in group B.

Comparisons of the group parameters are given in Table 2. Groups were similar in terms of gender distribution and refractive errors. While the mean age was significantly higher in group A (p=0.006), the distant and near-deviation angles were significantly lower compared with group B. P values were 0.033 for the distant deviation angles and 0.012 for the near-deviation angles. Fourteen participants had a zero deviation angle on the prism-cover test, and 64% of these achieved an excellent stereoacuity level. The remaining 49 participants had latent deviations that changed from 1 to 35 PD, and only 26% of these achieved excellent stereoacuity. Latent deviation had a negative effect on the measured stereoacuity level, but how did the type of deviation affect the stereoacuity level? The deviation types were 67% exophoria and 33% orthophoria for group A, and 78% exophoria, 14% orthophoria, and 8% esophoria for group B. Pearson chi-square analyses did not show a significant difference between the groups regarding the distribution of the deviation types (p=0.077) (Table 2).

Table 1. Correlation between deviation angles and stereotest results

Stereotests	Statistics	Parameters		
		Age	Near-deviation angle	Distant deviation angle
TNO	Pearson correlation	-0.261	0.380	0.132
	p	0.039	0.002	0.304
Titmus	Pearson correlation	-0.214	0.306	0.029
	p	0.920	0.015	0.824

DISCUSSION

Individuals with bi-foveal fixation typically have 60 arcseconds and lower stereosensitivity thresholds, whereas 30 arcseconds and below are defined as excellent levels of stereosensitivity (13). In this study, participants were grouped as having either excellent stereosensitivity or not, and the effect of latent deviation achieving on excellent level stereosensitivity was evaluated. Forty-four percent of the group achieved an excellent stereoacuity level. Both TNO and Titmus stereothresholds tended to increase significantly as the latent deviation angles increased. However, the correlation was stronger for the TNO test. These results indicate that the latent deviation angle has a significant effect on the measured stereosensitivity level. Additional support for this argument is the observed higher retesting variability in subjects with higher near latent deviations. The decompensation of phoria at different levels of each stereotesting might cause the variability measured on the stereosensitivity level. Fender and Julesz (14) studied Panum's fusional areas for random-dot stereograms and found that images stimulating both eyes must be aligned within 6 min arc disparity before fusion can occur. Though study participants had fusion for both distance and near on the W4D test, they might have lost their alignment and manifested latent deviations during the testing period of

Table 2. Comparison of the group with excellent stereosensitivity (group A) with the group who could not achieve excellent stereosensitivity (group B)

Parameters	Group A n=27	Group B n=36	p
Age (years)	29.14±5.57	25.47±4.60	0.006
Sex (F/M)	22/5	23/13	0.126
Refraction (diopter)	-1.07±1.32	-1.06±1.54	0.395
Eso/exo/orthophoria (%)	0/67/33	8/78/14	0.077
Near-deviation (prism diopter)	3.07±3.26	6.50±6.92	0.012
Distant deviation (prism diopter)	2.51±3.06	5.38±6.28	0.033
TNO (arcseconds)	24.44±7.38	99.44±97.91	0.000
Titmus (arcseconds)	42.22±11.24	52.22±31.81	0.089

F: Female, M: Male, Eso: Esophoria, Exo: Exophoria

stereopsis. Performing the W4D test takes a few seconds, but performing the TNO test takes 3-5 minutes and can lead to decompensated phoria.

Experimental studies investigating the effect of fusional stress on stereoacuity were done by simulating heterophoria using base-out prisms or Synoptophore. Laird et al. (15) observed degradation of stereoacuity as the convergence stress increased with base-out prisms. However, Tidbury et al. (16) did a similar study using Synoptophore instead of prisms and found no effect of convergence stress on stereoacuity if the phoria was well controlled. Both investigators compared baseline stereoacuities with the stereoacuities at the fusion recovery limits. The median fusion recovery limit was 20 (±4) PD for the Laird's group, whereas it was 8 (±6) PD for the Tidbury's group. Differences in their methodology might have caused the significantly different median fusion recovery limits and opposite results.

Archer et al. (17) evaluated vergence amplitudes with an amblyoscope using monocular and random-dot targets. They showed that random-dot stereograms could produce fusional vergence amplitudes once fusion had been obtained. They observed similar fusional vergence break-up amplitudes with random-dot and monocular targets. However, fusional recovery was more difficult or not possible for some subjects in random-dot targets. Similarly, subjects with latent deviations must recover fusion if their deviations are manifested during the stereotesting procedure; otherwise, no stereosensitivity can be measured.

Higher stereosensitivity thresholds up to 120 arcseconds were reported with the TNO test (18,19). In this study, the mean stereosensitivity thresholds obtained with TNO and Titmus tests were 67 (±83) and 48 (±25) arcseconds, respectively. Despite full vision in both eyes, orthotropia, and fusion in the W4D test, four subjects had stereosensitivity thresholds over 60 arcseconds in both tests. The common feature of these subjects was the convergence-divergence imbalance for near fixation. The coupling of convergence-divergence imbalance with the disassociating effect of stereotesting might have led to the degradation of stereosensitivity thresholds. This condition corresponds to the diminished distant stereosensitivity thresholds in exophoric subjects who started to decompensate (20,21).

An interesting result obtained in the study was that the group with an older average age showed improved stereosensitivity. The main explanation for this observation was this group's lower average deviation angle. Studies evaluating the effect of age on stereosensitivity report two different results: Age has no effect on stereosensitivity (22) and stereosensitivity decreases with age (3,23,24). But most of these studies have evaluated only age groups over 60 years. Garnham and Sloper (23) evaluated stereosensitivity in normal subjects aged 17-83 years and observed some decline in stereosensitivity with age by all tests. The decline started over 30 years of age for TNO and over 50 for the Titmus test. They also detected a small decline with age in the fusional divergence range for distance, but this change did not explain the stereosensitivity decline in their group. They suggested that the reduction found in these older subjects using a random-dot test might have been caused by an actual loss of stereosensitivity at the cortical level. The upper age range was 35 years in this study. There were 18 participants over 30 years of age, and most of them had stereosensitivities over the group average. Since all of them were ophthalmologists or ophthalmology residents, they might have shown an expert performance in the stereotests.

Another subject to be determined is the effect of deviation type on stereoacuity. As is known, divergence control mechanisms are stronger. In addition to the stronger fusional convergence amplitudes, accommodative, proximal, and tonic convergence mechanisms are also active at close fixation (25). Besides, whereas convergence is an active movement, divergence is passive, which occurs with the loosening of convergence (25). Decompensation of the exophoria could be compensated for by an innate convergence effort of the eyes to capture the fusible stereotarget. However, esophoria decompensation might be difficult to compensate for in the disassociated conditions of stereotesting. So, it might be expected that stereosensitivities of esophoric subjects are more fragile under disassociated conditions. None of the esophoric participants achieved an excellent level of stereoacuity in this study group. On the other hand, esophoria was a rare condition, and only 3 (5%) of the participants were esophoric.

The weak point of this study is an inadequate representation of esophoric subjects in the group. Though we had some clues showing the negative effect of convergent latent deviation on stereoacuity, we could not prove it with significant power.

CONCLUSION

Our results demonstrated that latent deviation angles could mask true stereosensitivity potentials of subjects to some extent during the stereotesting procedure.

Ethics

Ethics Committee Approval: Ethics Committee of İzmir Katip Çelebi University (decision number: 56, date: 06.02.2019).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL ARTICLE

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Effects of Oral or Parenteral Vitamin D Supplementation on Kidney Function, Blood Concentrations of 25-Hydroxyvitamin D, and Parathyroid Hormone Levels

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Abstract

Objective: The aim of this study was to determine the effects of vitamin D supplementation on kidney function, blood concentrations of 25-hydroxyvitamin D, and parathyroid hormone levels.

Methods: The 25-hydroxyvitamin D levels of approximately 4,000 participants between the ages of 18 and 75 years were investigated retrospectively. Inclusion criteria included screening 25-hydroxyvitamin D <10 ng/mL at the local clinical laboratory. This study required the control of blood parameters at 2 and 6 weeks. Because of this, 120 patients were chosen and categorized according to treatment procedures. The first group of participants was prescribed a fixed dose of 300,000 IU oral vitamin D filled at local clinical pharmacies. The second group of participants was prescribed a fixed dose of 300,000 IU parenteral vitamin D filled at local clinical pharmacies. The last group of participants was prescribed a fixed dose of 50,000 IU once weekly oral vitamin D once weekly for six weeks filled at local clinical pharmacies. Vitamin D values and biochemical laboratory parameters were recorded and were compared between groups using statistical methods.

Results: The treatment regimens with 25-hydroxyvitamin D3 were divided equally among three patient groups (n1=40, n2=40, n3=40). The findings were that 25-hydroxyvitamin D levels changes in the first (p=0.001) and third groups (p=0.001) were greater than the second group (p<0.01).

Conclusion: These effects occur with significant changes in oral vitamin D supplementation rather than when vitamin D is administered parenterally.

Keywords: Vitamin D, calcium, oral, parenteral

INTRODUCTION

Vitamin D is synthesized in the body with the effect of 90%-95% of sunlight. Besides, it can be dissolved in oils from the intake of dietary sources. It physically looks like some hormones such as testosterone, estrogen, cortisol, and others (1-3). During the last 2 decades, vitamin D has been recognized for having very positive effects on the immune system and the cardiovascular system (4).

Vitamin D deficiency, which affects about one million people, is a public health problem. Intake from the diet is limited. It exists as cholecalciferol (D3) and ergocalciferol (D2) and is found in the diet mostly in fatty fish, such as salmon and egg yolks (5). Reasons for the deficiency include altitude, season, cultural malnutrition, clothing style, domestic lifestyle, skin pigmentation, tuberculosis, some drugs, and genetics (2). Deficiency can be restrained by low-cost intake (6). Although it

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does not have an exact definition, the level of 25-hydroxyvitamin D [25 (OH) D] is a standard parameter used to indicate accurate vitamin D levels (7). As a treatment, D3 is much more suitable than D2. Moreover, treatment can be taken for daily support (8) because low circulating concentrations of 25 (OH) D are common, and a deficiency in 25 (OH) D may contribute to adverse health outcomes. Despite widespread use, the effects of vitamin D supplements on downstream vitamin D metabolism are unclear. According to the literature, vitamin D filled at local clinical pharmacies at 50,000 IU once weekly for 6-8 weeks can achieve circulating concentrations of 25 (OH) D of at least 30 ng/mL (9).

According to studies, vitamin D deficiency's treatment is not clear. Oral or parenteral methods are controversial (10). Also, the information regarding the bioavailability of parenteral treatment is limited. Because of this, our study is based on the circulating concentrations of 25 (OH) D, parathyroid hormone (PTH), and kidney function (spot urine sample).

METHODS

This study was approved by the institutional review boards of Okmeydani Training and Research Hospital in 2019 (approvel no: 02.04.2019-1227). The study was initiated before adopting the expanded definition of a clinical trial by the International Committee of Medical Journal Editors in 2018. It was considered at the time to be a detailed physiologic study rather than a clinical trial. For this reason, it was not prospectively entered into a clinical trials registry. Between 2018 and 2019, approximately 4,000 participants between 18 and 75 were recruited from the Okmeydani Training and Research Hospital outpatient physiotherapy clinics. Their 25 (OH) D levels were investigated retrospectively. All potential candidates showing interest in the study were invited to attend a screening visit, at which eligibility for inclusion was assessed, and informed consent was obtained. Inclusion criteria included screening 25 (OH) D <10 ng/mL at the local clinical laboratory. This study required controlling blood parameters [glucose, urea, creatinine, calcium (Ca), potassium, alp, PTH] at 2 and 6 weeks was needed. Because of this, 120 patients were chosen and categorized according to treatment procedures. The exclusion criteria are hypercalcemia-hypercalciuria, chronic kidney failure, kidney stones, using any drugs that affect vitamin D and bone metabolism, geographic information systems disease (malabsorption), osteoporosis treatment, malignancy, diabetes mellitus, hyperthyroidism, cancer, rheumatoid arthritis, chronic drug use, and alcohol abuse.

The first group of participants was prescribed a fixed dose of 300,000 oral vitamin D filled at local clinical pharmacies. The second group of participants was prescribed a fixed dose of 300,000 parenteral vitamin D filled at local clinical pharmacies. The last group of participants was prescribed a fixed dose of 50,000 IU oral vitamin D once weekly for 6 weeks, filled at local clinical pharmacies.

Measurements of laboratory tests: Glucose, urea, creatinine, phosphorus, and Ca tests were measured with the calorimetric method, PTH, and 25-hydroxyvitamin D3 values were measured with chemiluminescence method in an autoanalyser (BeckmanCoulter TM, AU 5800 model, USA).

Statistical Analyses

Descriptive statistics were used to compare baseline participant characteristics. The number cruncher statistical system 2007 (Kaysville, Utah, USA) was used for these analyses. The Shapiro-Wilk test was used to assess the normality of outcomes distribution. The statistical evaluation of the three groups involved applying the One-Way ANOVA test and Bonferroni test that were chosen for parametric variables. The other variables were assessed with the Kruskal-Wallis test and Bonferroni-Dunn test. The Wilcoxon signed-rank test was used for the first and sixth-week comparisons of variables that did not show a normal distribution. The repeated measures test was used for the first, second, and sixth-week comparisons of normally distributed variables, and the Bonferroni test was used for binary comparisons. The Friedman test was used for the first, second, and sixth-week comparisons of variables that did not show a normal distribution. The Bonferroni-Dunn test was used for binary comparisons. Qualitative data comparisons were made using Pearson's chi-square test, and the Fisher-Freeman-Halton test was used. Spearman Rho and Pearson correlation tests were used to determine correlations between the variables tested. For all the calculations in the study, a p value less than 0.05 was considered statistically significant.

RESULTS

In our study of 120 patients, vitamin D was administered intermittently in 33.3% (n=40) of the cases, by intramuscular (IM) in 33.3% (n=40), by mouth in 33.3% (n=40). Women comprised 79.2% (n=95) of the cases and men comprised 20.8% (n=25) of the cases. The body mass index scale was between 17.2 and 42.2 with an average of 26.79+4.36. Regarding educational level, 5.8% (n=7) were illiterate, 8.3% (n=10) were literate, 62.5% (n=75) graduated from primary school, 15.1% (n=18) graduated from high school, and 8.3% (n=10) graduated from a university.

The dependency on the duration of physical activity was observed in: 24.2% (n=29) less than an hour per week, 34.1% (n=41) 1-2 hours per week, 4.2% (n=5) 4-7 hours per week, and 7.5% (n=9) 7 hours per week.

Concerning sunbathing, 70.0% (n=84) less than an hour per week, 14.2% (n=17) 1-2 hours per week, 5.8% (n=7) 2-4 hours per week, 4.2% (n=5) 4-7 hours per week, and 5.8% (n=7) 7 hours per week.

Regarding Ca intake: 14.2% (n=17) of cases do not take any at all; the rest of them take Ca.

Concerning smoking: 21.7% (n=26) of cases have a smoking habit, the rest do not use tobacco.

When asked about clothing style, answers were: 1.7% (n=2) local style, 43.3% (n=52) modern style, and 55% (n=66) closed style.

For all the calculations in the study, a p value less than 0.05 was considered statistically significant. Educational level (p=0.002; p<0.01), physical activity frequencies (p=0.004; p<0.01), and Ca intake are statistically significant.

Evaluation of the level of vitamin D: According to the groups, there was no statistically significant difference (p=0.995; p>0.05).

According to the groups, the sixth-week measurement of vitamin D is statistically significant (p=0.001). The correlation between the groups' vitamin D intake by oral, intermittent, and IM is statistically significant (p<0.05). Oral and intermittent intake forms have an advantage on intake.

All three groups sixth-week measurements are statistically significant (intermittent p=0.001, IM p=0.001, oral p=0.001).

The evaluation of the level of PTH: According to the groups, there was no statistically significant difference between the first (p=0.883) and sixth-week levels (p=0.358).

All three groups' sixth-week levels decrease is statistically significant (intermittent p=0.01, IM p=0.002, oral p<0.01).

There is not any differences between groups sixth-week results (p=0.197; p>0.05) (Table 1).

According to the groups, first and sixth-week circulating Ca levels changes are not significant as statistically (p>0.05).

Table 1. According to vitamin D groups, evaluation of circulating concentrations of PTH, vitamin D, and phosphorus levels

		Type of vitamin D intake			[b]p
		Intermittent (n=40)	IM (n=40)	Oral (n=40)	
1st vitamin D	Min-max (median)	2-10 (8.3)	1.4-10 (8.2)	2.3-10 (8)	0.995
	Average ± SD	7.66±2.05	7.64±2.02	7.61±2.04	
6th week	Min-max (median)	19.7-80.2 (43.8)	14-57.5 (25)	23.9-77 (45.5)	0.001**
	Average ± SD	43.65±11.79	25.06±8.57	46.32±11.49	
	[e]p	0.001**	001**	0.001**	
Difference	Min-max (median)	11.2-73.9 (37)	6.6-49.7 (16.7)	13.9-69.9 (36.4)	0.001**
	Average ± SD	35.99±11.54	17.42±8.71	38.71±11.87	
1st PTH	Min-max (median)	22.8-125.4 (55)	20.9-114 (60)	22-124 (53.6)	0.883
	Average ± SD	58.05±22.52	59.66±21.29	58.80±22.83	
6th week	Min-max (median)	18.1-79.4 (47.6)	18.8-70 (41.5)	30.9-89.1 (45.5)	0.358
	Average ± SD	45.61±14.39	43.48±13.40	48.00±11.84	
	[e]p	0.001**	0.001**	0.002**	
Difference	Min-max (median)	-76.2-22.5 (-7.9)	-60.1-15.7 (-14)	-70-24.9 (-4.7)	0.197
	Average ± SD	-12.44±18.98	-16.18±16.95	-10.80±20.04	
1st phosphorus	Min-max (median)	2.6-4.6 (3.6)	2.5-8.5 (3.6)	2.7-4.6 (3.6)	0.626
	Average ± SD	3.63±0.50	3.63±0.93	3.63±0.44	
6th week	Min-max (median)	3-4.9 (3.5)	3-5 (3.8)	3.1-4.6 (3.8)	0.149
	Average ± SD	3.64±0.51	3.76±0.41	3.80±0.39	
	[e]p	0.877	0.010*	0.010*	
Difference	Min-max (median)	-1-0.9 (0)	-4.6-1.3 (0.3)	-0.7-0.9 (0.2)	0.194
	Average ± SD	0.01±0.55	0.12±0.91	0.17±0.41	

[b]Kruskal-Wallis test, [e]Wilcoxon Signed-Rank test, *p<0.05, **p<0.01, PTH: Parathyroid hormone, SD: Standard deviation, IM: Intramuscular, Min: Minimum, Max: Maximum

second circulating Ca levels are statistically significant to each other (p=0.009). Intake of vitamin D by oral is much more effective than by IM intake (p=0.007).

Second measurements are significant to each other (p=0.003). Intake of vitamin D by oral is much more effective than by IM intake (p<0.05).

The evaluation of the Ca level in urine: According to the groups, first and sixth-week urine Ca levels changes are not significant as statistically (p>0.05).

Sixth-week circulating Ca levels are statistically significant to each other. Intake of vitamin D by oral is much more effective than by IM intake (p=0.049) (Table 2).

The evaluation of Ca/Cre ratio in urine: According to groups, there is not any significant difference between first, second, and sixth measurement (p=0.945; p=0.871; p=0.972).

Regarding the difference between measurement times, there is no statistically significant difference (Table 3).

DISCUSSION

Although the effects of vitamin D and deficiency are well known, there is no definite opinion on the effectiveness of the forms to be used in treatment. There are many studies on the effectiveness and ease of use of oral or parenteral forms, and each reported different results (8-11).

Table 2. According to vitamin D groups, evaluation of circulating and urine concentrations of calcium

		Vitamin D intake			[b]p
		Intermittent (n=40)	IM (n=40)	Oral (n=40)	
1st circulating Ca	Min-max (median)	8.8-10.3 (9.6)	8.7-10.4 (9.7)	8.5-10.5 (9.6)	[a]0.949
	Average ± SD	9.58±0.36	9.60±0.42	9.57±0.38	
2nd circulating Ca	Min-max (median)	9-10.8 (9.6)	7-10.3 (9.5)	8.9-10.7 (9.7)	[a]0.009**
	Average ± SD	9.58±0.42	9.43±0.56	9.74±0.33	
6th week circulating Ca	Min-max (median)	8.8-10.5 (9.6)	8.8-10.2 (9.5)	8.4-10.3 (9.7)	[a]0.157
	Average ± SD	9.53±0.40	9.47±0.38	9.63±0.33	
	[f]p	0.709	0.117	0.002**	
Difference (2nd-1st)	Min-max (median)	-0.9-1.1 (-0.1)	-2.4-0.8 (-0.1)	-0.5-1.1 (0.2)	0.003**
	Average ± SD	-0.01±0.44	-0.17±0.59	0.17±0.29	
Difference (6th-1st)	Min-max (median)	-1-1.1 (-0.1)	-1.1-0.6 (-0.1)	-0.4-0.7 (0.1)	0.121
	Average ± SD	-0.05±0.44	-0.13±0.45	0.05±0.26	
Difference (6th-2nd)	Min-max (median)	-1.3-0.8 (-0.1)	-0.9-1.9 (0)	-1.2-0.6 (-0.1)	0.518
	Average ± SD	-0.05±0.46	0.03±0.54	-0.12±0.33	
First urine Ca	Min-max (median)	3.1-22.7 (9)	3.9-19.8 (8.1)	3.2-21.2 (7.6)	0.984
	Average ± SD	9.21±5.08	9.22±4.79	9.05±4.9	
2nd urine Ca	Min-max (median)	4.2-23.4 (9.8)	1.2-29.8 (11)	3.1-31.7 (11.4)	0.944
	Average ± SD	11.57±5.55	12.17±7.62	11.87±7.38	
6th week urine Ca	Min-max (median)	1.6-30 (10)	4.1-46.4 (9.7)	3.4-23.8 (8.8)	0.728
	Average ± SD	10.33±6.19	12.09±8.33	11.41±6.72	
	[g]p	0.049*	0.023*	0.741	
Difference (2nd-1st)	Min-max (median)	-13.6-12.3 (3)	-13.1-20.3 (2.1)	-17.1-21.8 (3)	0.997
	Average ± SD	2.36±4.8	2.95±7.87	2.81±8.47	
Difference (6th-1st)	Min-max (median)	-14.2-24.3 (1.4)	-11.3-30.6 (2.1)	-13.7-20.6 (0.1)	0.615
	Average ± SD	1.12±7.63	2.88±7.31	2.36±8.44	
Difference (6th-2nd)	Min-max (median)	-15.3-18.5 (-1)	-13.1-16.7 (0.7)	-17.4-18.7 (0.4)	0.805
	Average ± SD	-1.24±6.95	-0.08±6.53	-0.45±8.09	

[a]One-Way ANOVA test, [b]Kruskal-Wallis test, [f]Repeated Measures test, Freidman test, *p<0.05, **p<0.01, Ca: Calcium, SD: Standard deviation, IM: Intramuscular, Min: Minimum, Max: Maximum

In recent years, research on vitamin D as randomized controlled studies on vitamin D replacement has increased. Between 2003 and 2017, there was a higher increase in publications scanned as "vitamin D supplementation" in PubMed compared with all studies on vitamin D. It is estimated that this number will increase even more with more than 100 randomized controlled vitamin D replacement studies registered in the ClinicalTrals.gov system (11).

We planned this study based on this increase. This study aimed to evaluate the effects of oral, intermittent oral, and parenteral 25 (OH) D replacement on vitamin D blood levels, PTH levels, and kidney function.

In this study, the increase in the sixth-week measurements was statistically significant compared with the first measurements of vitamin D in all three groups. Intermittent oral and single dose orally administered vitamin D measurements at six weeks between groups were higher than those receiving vitamin D intramuscularly. However, there was no statistically significant difference between the measurements of the groups taking intermittent oral and single dose oral vitamin D. Gupta et al. (12) investigated the effect of oral (5 weeks of 60,000 IU) and IM (300,000 IU) vitamin D replacement in the treatment of vitamin D deficiency. They detected a significant increase in vitamin D in both groups at the end of the sixth-week.

Whyte et al. (13) reported that oral or intravenous (IV) forms showed a definite increase in a week in their study comparing different vitamin D forms in healthy adults. This increase in IM and subcutaneous forms occurred only in the seventh week, and vitamin D levels decreased in oral or IV form in the same period. In our study, oral forms had a more significant increase at the end of the sixth-week than those who used IM forms. It may be because this study was conducted using healthy adults might have caused a difference in bioavailability times between our study when compared with those with vitamin D deficiency.

In their study, Zabihiyeganeh et al. (14) compared vitamin D administered as a single dose 300,000 IU IM injection and six doses of 50,000 IU oral D3 vitamin D in the treatment of hypovitaminosis D. In the 3rd month, the 25 (OH) D vitamin level was significantly higher than that given by the oral route, similar to our study. However, Zabihiyeganeh et al. (14) reported that the sixth-month measurements were similar.

Tellioglu et al. (15) evaluated 116 nursing home residents aged 65 and over. Of these, 600,000 IU D3 were administered IM or orally to 66 people whose 25 (OH) D level was found below <30 ng/mL. They evaluated the biochemical results at 6 and 12 weeks. Although the results at 6 weeks were consistent with our study results, at 12 weeks, the increase in the 25 (OH) D level of the IM group was significantly higher than the oral group.

PTH levels are expected to be high in patients with vitamin D deficiency (16). In our study, the first measurements in the intermittent oral group (58.05±22.52 pg mL) were not significantly higher than in the IM group (59.66±21.29 pg/mL) and in the dose oral group (58.80±22.83 pg/mL). In their study, Sahota et al. (17) reported that vitamin D deficiency did not increase PTH value in some cases. However, PTH levels at six weeks in all groups in our study were found to be significantly

Table 3. According to vitamin D groups, evaluation of urine concentrations of calcium/creatinine level

		Vitamin D intake			[b]p
		Intermittent (n=40)	IM (n=40)	Oral (n=40)	
1st Ca/Cre	Min-max (median)	0-0.1 (0.04)	0.01-0.09 (0.04)	0-0.1 (0.05)	0.945
	Average ± SD	0.05±0.03	0.05±0.02	0.05±0.03	
2nd Ca/Cre	Min-max (median)	0.01-0.1 (0.05)	0.01-0.1 (0.04)	0-0.1 (0.05)	0.871
	Average ± SD	0.05±0.03	0.05±0.03	0.05±0.03	
6th Ca/Cre	Min-max (median)	0.01-0.1 (0.04)	0.01-0.1 (0.04)	0-0.1 (0.04)	0.972
	Average ± SD	0.05±0.03	0.05±0.03	0.05±0.03	
	[g]p	0.684	0.282	0.921	
Difference (2nd-1st)	Min-max (median)	-0.07-0.09 (0)	-0.07-0.08 (0)	-0.07-0.07 (0)	0.890
	Average ± SD	0±0.04	0±0.04	0±0.03	
Difference (6th-1st)	Min-max (median)	-0.07-0.07 (0)	-0.07-0.08 (0)	-0.07-0.07 (0)	0.937
	Average ± SD	0±0.04	0±0,04	0±0.04	
Difference (6th-2nd)	Min-max (median)	-0.09-0.08 (0)	-0.07-0.09 (0)	-0.08-0.07 (0.01)	0.657
	Average ± SD	0±0.04	0±0.04	0±0.04	

[b]Kruskal-Wallis test, [g]Friedman test, Ca: Calcium, Cre: Creatinine, SD: Standard deviation, IM: Intramuscular, Min: Minimum, Max: Maximum

lower than the first measurements. There was no statistically significant difference between the groups regarding changes in the first- and sixth-week measurements. Leventis and Kiely (18) found a decrease in PTH levels because of 12 weeks of 300,000 IU IM and oral vitamin D treatment.

A significant difference was detected between the groups in the second-week blood Ca results after vitamin D support in our study. The change in the group receiving oral vitamin D was found to be significantly higher than the groups receiving vitamin D intermittently ($p=0.044$) and with the IM method ($p=0.004$; $p<0.05$).

An increase in blood Ca values was detected in the second-week measurements in all three groups. There was a statistically significant difference between the Ca measurements in the blood in the second-week, according to the groups ($p=0.009$; $p<0.01$). The measurements of the group receiving vitamin D orally are higher than the group receiving vitamin D with the IM method ($p=0.007$; $p<0.01$). No statistically significant difference was found in other binary comparisons ($p>0.05$). Blood Ca changes in the sixth-week measurements according to the first measurements, changes in the sixth-week measurements according to the second-week measurements were not statistically significant ($p>0.05$). In the treatment of vitamin D deficiency, blood Ca elevation is seen because of increased Ca absorption from the intestine and increased bone metabolism (19).

Spot Urine Ca/Kr ratio is a simple, low-cost, and reliable method used to calculate Ca excretion due to difficulties in 24-hour urine Ca level. In our study, we also used spot urine Ca/Kr excretion indices to determine hypercalciuria. In our study, values below 0.14 were normal, and values above were considered hypercalciuria. No patients had hypercalciuria. Leaf et al. (20) investigated the effect of vitamin D replacement on urinary Ca excretion by administering 50,000 IU D2 orally for eight weeks to patients with D hypovitaminosis with a history of nephrolithiasis. In their evaluation during the eighth week, they reported that, despite a significant increase in 25 (OH) D vitamin levels, the mean 24-hour urinary Ca excretion did not change. Similarly, there was a significant increase in 25 (OH) D levels in all three groups in our study, but no significant increase in mean spot urine Ca values.

Study Limitations

Our study has some limitations. The main limitations are that it is a retrospective study and the recorded follow-up times are relatively short. A longer follow-up period might contribute to a more meaningful evaluation of the effect of 25 (OH) D levels and the impact of IM vitamin D treatment. It was observed that all three forms of administration are quite effective and safe in treating hypovitaminosis D. Although oral therapy has been shown to increase the level of vitamin D significantly in our study, the mode of treatment may depend on patient selection and compliance.

CONCLUSION

It appears that inadequate vitamin D deficiency treatment leads to serious health problems, but treatment costs are relatively low. We think that prospective studies with high case numbers demonstrating the effectiveness of different forms of treatment will be beneficial.

Ethics

Ethics Committee Approval: Okmeydani Training and Research Hospital in 2019 (approvel no: 02.04.2019-1227).

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., O.D., Concept: S.A., Design: S.A., E.D., B.H., T.A., O.D., Ö.K., Data Collection or Processing: S.A., E.D., B.H., Analysis or Interpretation: S.A., E.D., B.H., O.D., Ö.K., Literature Search: S.A., T.A., Writing: S.A.

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ORIGINAL ARTICLE

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Inflammatory Markers in Hyperemesis Gravidarum

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Abstract

Objective: This study aims to investigate the role of inflammation in the pathophysiology of hyperemesis gravidarum (HEG).

Methods: This prospective study was conducted in the Department of Obstetrics and Gynecology at Near East University Hospital between July 2019 and March 2020. The patients that were defined as HEG should have the following symptoms: Persistent nausea and vomiting, loss of >5% of pre-pregnancy body weight, presence of at least one positive ketonuria test in a random urine analysis, fetal heartbeat positivity at 6-13 weeks of gestation, and singleton pregnancy. Total blood count including white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), hemoglobin, hematocrit, and platelet and red cell distribution width (RDW) and platelet distribution width were analyzed. NEU-to-LYM (NLR) and platelet-to-LYM ratios (PLR) were calculated.

Results: Forty-nine patients with HEG and 121 healthy women were evaluated in the first trimester of pregnancy. The healthy pregnant women and patients with HEG had similar age, gravida, parity, gestational weeks, and body mass index. WBC, NEU, RDW, C-reactive protein (CRP), and urinary ketone levels were statistically higher in the HEG group. There were no differences in terms of NLR or PLR.

Conclusion: Measurement of inflammatory markers, such as WBC, NLR, PLR, and CRP levels, might provide valuable knowledge in HEG diagnosis. NLR and PLR are acceptable, but CRP level is a better indicator for predicting the diagnosis and severity of the disease according to our study findings.

Keywords: Hyperemesis gravidarum, inflammation, C-reactive protein, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

INTRODUCTION

Nausea and vomiting are common symptoms seen in pregnancy (1). If the symptoms are mild, nausea in the first trimester can be considered as a part of normal physiological changes. Hyperemesis gravidarum (HEG), which is a severe form of nausea and vomiting in pregnancy, can cause electrolyte imbalance, dehydration, fluid and acid-base imbalance, nutrition deficiency, ketonuria, and loss of >5% of body weight (1,2). The incidence of nausea and vomiting is 85% in pregnancy, but only 0.3%-2% of pregnant women will have HEG (3,4). The etiopathogenesis of HEG has been evaluated in many studies, but the exact cause remains unclear. The disease is considered associated with multifactorial conditions, such as maternal endocrinological, immunological, and psychological factors. In addition, placental growing and pregestational gastrointestinal status may be related to the etiology (5). Risk factors for HEG include primigravida, multiple gestation, molar pregnancy, prior unsuccessful pregnancy, and prior HEG.

Researchers had shown that inflammation is a factor in the pathophysiology of the disease and is closely related to the severity of the symptoms. The present data are not enough to explain the role of inflammation in HEG pathogenesis, but inflammation may be associated with the onset of the HEG. In literature, the role of proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), has been comprehensively evaluated in HEG pathogenesis and were associated with the disease (6,7). Different hematological parameters have been used to evaluate the inflammatory status of distinct disease states recently. Mean platelet volume (MPV), platelet distribution width (PDW),

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neutrophil-to-lymphocyte ratio (NLR), red cell distribution width (RDW), and platelet-to-lymphocyte ratio (PLR) are simple markers shown to reflect inflammation and disease activity in several disorders, including ulcerative colitis, spontaneous bacterial peritonitis, malignancies, and cardiovascular diseases (8,9). Oxidative stress is an instability of oxidant molecules and antioxidant defenses in humans and this imbalance may result in pathological situations that include pregnancy and complications about pregnancy. It is thought that oxidative stress, which accompanies subclinical inflammation, may trigger the onset of HEG (9).

This study aims to investigate the diagnostic value of MPV, PDW, NLR, RDW, PLR, and CRP in patients with HEG.

METHODS

This prospective study was conducted in the Department of Obstetrics and Gynecology at Near East University Hospital, Faculty of Medicine, Nicosia, Cyprus, between July 2019 and March 2020 (date: 25.07.2019, 2019/71, 877). The study protocol was approved by our institutional review board, and an informed consent was obtained from all patients. A total of 49 patients with HEG and 121 healthy gestational age-matched control subjects were studied. The patients that were defined as HEG should have the following symptoms: Persistent nausea and vomiting, loss of >5% of pre-pregnancy body weight, presence of at least one positive ketonuria test in a random urine analysis, fetal heartbeat positivity at 6-13 weeks of gestation, and singleton pregnancy. Patients with HEG were not classified into subgroups because the group consisted of patients with mild HEG. Patients who had multiple gestations, cigarette smoking, chronic diseases, thyroid disorders, gastrointestinal disorders, or urinary infections were excluded. Age, body mass index, gestational age, gravidity, and parity of each patient were recorded. The gestational age was determined by using the date of the last menstrual period, and it was confirmed by ultrasonography. Body mass index was calculated by dividing body weight in kilograms by the square of height in meters.

Total blood count including white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), hemoglobin, hematocrit, and platelet and RDW and PDW were analyzed. NLR and PLR were calculated. Using differential count, NLR was calculated by dividing the absolute NEU count by the absolute LYM count. PLR was calculated by dividing platelet count by the LYM count. Urine ketone levels, CRP, and thyroid-stimulating hormone levels were also recorded. The ketonuria was graded as 1+, 2+, and 3+.

Statistical Analysis

Statistical Program for Social Sciences (SPSS) version 16 (SPSS, Chicago, IL) was used for data analysis. Homogeneity of continuous variables was assessed using Shapiro-Wilk test. HEG and control patients' values were compared using independent t-test. Data were expressed as mean ± standard deviation. Gestational age, gravida, and parity were analyzed using Mann-Whitney U test, and the results are given as median (minimum-maximum). Multivariate analysis was performed for PLR, RDW, and CRP, WBC, and NEU counts. Receiver operating characteristic (ROC) curves are drawn for CRP and NEU count. $P<0.05$ was considered to be statistically significant.

RESULTS

The results of 170 patients were evaluated. Forty-nine patients had HEG, and 121 were healthy women in the first trimester of pregnancy. Table 1 shows a comparison of demographic characteristics between patients with HEG and healthy controls. The healthy pregnant women and patients with HEG had a similar age, gravida, parity, gestational weeks, and body mass index. Table 2 shows the univariate analysis of the comparison of laboratory findings between patients with HEG and healthy controls. WBC, NEU, and CRP levels and RDW were statistically higher in the HEG group according to the univariate analysis (Table 2). Urinary ketone levels were evaluated by the chi-square test, and it was statistically significantly high in the HEG group compared with the control group ($p=0.014$). There were no differences in terms of NLR or PLR between HEG and healthy pregnant women. When we performed a multivariate analysis only, CRP levels were statistically high for patients with HEG ($p<0.001$). Since the multivariate analysis was significant for CRP levels only, we drew the ROC curve for CRP as shown in Figure 1. Table 3 illustrates the sensitivity and specificity for CRP in the diagnosis of HEG.

Table 1. Comparison of demographic findings

	Healthy control subjects (n=121)	HEG (n=49)	*p
[a]Age (years)	29.22±6.00	28.10±4.87	0.247
[b]Gravida	1 (1-6)	1 (1-3)	0.894
[b]Parity	0 (0-3)	0 (0-2)	0.931
[a]Gestational weeks	7 (6-13)	7 (6-13)	0.457
[a]BMI (kg/m^2)	23.18±1.28	22.54±1.98	0.319

The results are given as median (minimum-maximum). *p<0.05 is significant, [a]Independent t-test, [b]Mann-Whitney U test. BMI: Body mass index, HEG: Hyperemesis gravidarum

DISCUSSION

Inflammation and oxidative stress play an important role in the pathophysiology of HEG (7,8). NLR, PLR, and CRP are markers that reflect acute and chronic inflammation. Therefore, the study aimed was to compare and evaluate the inflammatory markers in pregnant women with HEG and healthy pregnant women. Our findings revealed that WBC, NEU, and serum CRP levels were statistically significantly high in patients with HEG compared with healthy controls. There was no difference in terms of NLR or PLR. Beyazit et al. (10) assessed 54 patients with HEG and 58 healthy controls. Their study results showed an increase in NLR and PLR in patients with HEG. Beyazit et al. (10) explained that NLR and PLR were elevated due to a physiological immune response of circulating leukocytes to HEG-associated physical stress, which results in amplification of NEU and decrease in LYM counts. Kan et al. (11) evaluated 113 patients with HEG and 41 healthy controls. In Kan et al.'s (11) study, markedly higher inflammatory markers, NLR, PLR, and CRP levels were found in patients with HEG compared with individuals who did not experience nausea or vomiting. This elevation of NEU and platelet levels in complete blood counts may be explained by the augmented inflammation process in HEG pathophysiology. In addition, Kan et al. (11) divided the patients into mild, moderate, and severe according to the symptoms. The severe group had the highest levels of CRP and NLR and PLR, but only CRP showed a statistically significant positive correlation with the severity of the disease (11). Our study findings of elevated NEU and serum CRP levels promote the base of inflammation process in the pathophysiology of HEG. However, we could not show the raised levels of NLR and PLR in our results. This may be due to the new onset of HEG symptoms and severity of nausea and vomiting because our study groups were mostly formed from patients with mild or moderate HEG symptoms.

Platelets are dynamic blood particles whose primary function, along with the coagulation factors, is hemostasis or prevention of bleeding. Platelets interact with each other, as well as with leukocyte and endothelial cells, searching for sites of injury, where they become activated (12). In pregnancy, platelets

Table 2. Laboratory findings

	Healthy control subjects (n=121)	HEG (n=49)	*p
Hb (g/dL)	12.22±1.18	12.36±1.23	0.487
Htc (%)	38.29±3.42	38.52±3.53	0.698
WBC ($mm^3/10^3$)	7.9 8±2.05	8.73±1.86	**0.027**
NEU ($mm^3/10^3$)	5.32±1.55	5.93±1.52	**0.019**
LYM ($mm^3/10^3$)	2.04±0.53	2.15±0.48	0.208
PLT ($mm^3/10^3$)	236.00±53.22	251.00±56.05	0.096
NLR	2.77±1.03	2.81±0.69	0.767
PLR	122.78±41.00	121.75±36.37	0.879
PDW (%)	19.11±1.25	19.41±1.11	0.150
RDW (%)	12.20±1.11	12.64±1.06	0.018
MPV (fL)	8.57±1.42	8.39±0.98	0.348
CRP (mg/L)	0.51±0.42	2.00±0.84	**<0.001**
TSH (mIU/L)	1.45±0.97	1.36±0.75	0.578

Independent t-test. *p<0.05 is significant, Hb: Hemoglobin, Htc: Hematocrit, WBC: White blood cells, NEU: Neutrophils, LYM: Lymphocyte, PLT: Platelet count, NLR: Neutrophil-to-lymphocyte ratio, MPV: Mean platelet volume, PLR: Platelet-to-lymphocyte ratio, PDW: Platelet distribution width, RDW: Red cell distribution width, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, HEG: Hyperemesis gravidarum

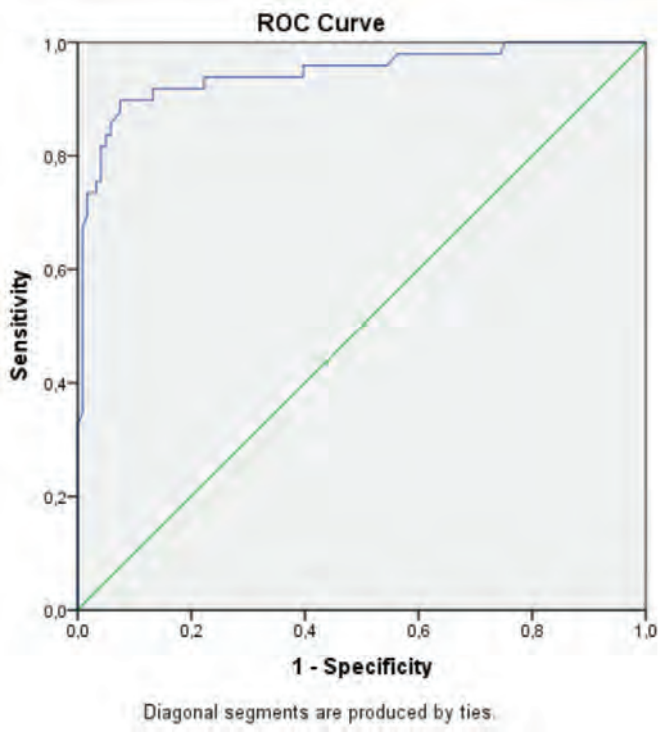

Figure 1. ROC curve for CRP
ROC: Receiver operating characteristic, CRP: C-reactive protein

Table 3. ROC data results for CRP and neutrophil count

Parameter	AUC	95% CI	SE	Cut-off v value	Sensitivity	Specificity	*p
CRP	0.946	0.90-0.99	0.021	1 (mg/L)	90%	91%	<0.001

*Statistically significant (p<0.05), ROC: Receiver operating characteristic, CRP: C-reactive protein, AUC: Area under the curve, SE: Standard error, CI: Confidence interval

may be affected by many factors other than the inflammatory processes, such as hemodilution and aggregation, and these factors are generally reflected in laboratory data as a decrease. In addition, hormones, such as estrogen, whose levels increase during pregnancy, can affect platelet functions and contribute to hypercoagulability. Evidence demonstrates that platelets contribute to the inflammatory process, microbial host defense, wound healing, angiogenesis, and remodeling (13). Platelet activation can be related to platelet size. MPV and PDW reflect platelet size and activation. They are from the most widely used surrogate markers of platelet function and have been shown to reflect inflammation (14,15). In literature, there is only one study to observe the relationship between MPV and PDW and existence of HEG (10). Beyazit et al. (10) found no significant difference in MPV and PDW in patients with HEG compared with healthy controls, which is in accordance with our study findings. In our study, MPV and PDW showed no statistically significant difference in patients with HEG and healthy controls, which puts forward that there should be pathological pathways related to HEG other than platelet activation.

Study Limitations

The limitations of this study are as follows. The first major limitation is that, in our study, the patients had mild-to-moderate HEG symptoms. Second, it would be worthwhile to study the serum levels of well-demonstrated proinflammatory markers, such as ILs and TNF-α, as this would give more understanding to the pathophysiology of HEG, if oxidative markers would be assessed and compared in patients with HEG. Alternatively, one of the major strengths of our study is the availability of complete data for each patient and exclusion of patients with risk factors for HEG, such as the presence of chronic and systemic endocrine, immunologic, or gastrointestinal disease.

CONCLUSION

Measurement of inflammatory markers, such as WBC and CRP levels and NLR and PLR might provide valuable knowledge in HEG diagnosis because inflammation contributes to the pathophysiology of HEG. NLR and PLR are acceptable, but CRP level is a better indicator for predicting the diagnosis and severity of the disease according to our study findings.

Ethics

Ethics Committee Approval: This prospective study was conducted in the Department of Obstetrics and Gynecology at Near East University Hospital, Faculty of Medicine, Nicosia, Cyprus, between July 2019 and March 2020 (date: 25.07.2019, 2019/71, 877).

Informed Consent: Was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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Thyroid Cancer Prevalence and Risk in Incidental Thyroid Lesions Detected with ^{18}F-FDG PET/CT

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Abstract

Objective: The aim of this study is to analyze the relationship between thyroid nodules detected in patients who were examined in our clinic for any indication and had ^{18}fluoro-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) scanning and thyroid cancer.

Methods: Results of patients who had FDG PET/CT scanning for any indication other than thyroid cancer during 2015 and 2016 in Okmeydani Training and Research Hospital were examined. Age and genders of patients, FDG PET scanning indications, FDG accumulation type (focal or diffuse), lesion maximum standard uptake value (SUV_{max}), histology, and pathology of the patient who had fine-needle aspiration biopsy (FNAB) or surgery were recorded. According to the results obtained from these values, the relationship between thyroid nodules and thyroid cancer was analyzed.

Results: Among the group of 50 patients, ^{18}F-FDG PET/CT scanning detected all as having thyroid nodules. Forty cases had benign diagnoses, whereas ten cases had malignant diagnoses either by FNAB or total thyroidectomy. According to the diagnosis results, the SUV_{max} average of the malignant group was higher than the SUV_{max} average of the benign group. However, no statistically significant result was obtained ($p>0.05$). The results also showed no statistically significant association regarding tumor size between the malignant and benign groups ($p>0.05$).

Conclusion: Thyroid incidentaloma was detected among patients who had ^{18}F-FDG PET/CT scanning for any reason other than thyroid cancer. Thyroid malignancy was detected in 20% of patients diagnosed with thyroid nodules by with focal ^{18}F-FDG accumulation. No statistically significant results concerning SUV_{max} value and lesion size were obtained among groups having benign and malignant diagnoses. Since no significant results were obtained between the SUV_{max} and malignancy, no threshold value for SUV_{max} was calculated.

Keywords: Thyroid nodules, incidentaloma, FDG PET/CT

INTRODUCTION

A nodule detected in the thyroid gland in imaging studies performed for different reason without PURPOSE imaging (1). ^{18}Fluoro-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is a valuable imaging method used for diagnosis, staging, restaging, treatment response, and biopsy guidance in oncological diseases (2).

A normal thyroid gland does not exhibit any physiological ^{18}F-FDG uptake. However, in approximately 1.2% to 4.3% of the ^{18}F-FDG PET studies, diffuse, or focal ^{18}F-FDG uptake is observed incidentally (1-3). In this examination, 14% to 50% of cases with focal involvement have thyroid malignancy, and those with diffuse involvement have diffuse hyperthyroidism or thyroiditis (1-3). In a review article, the malignancy rate was 4.4% for diffuse involvement and 34.8% for focal involvement (4). Most

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studies conducted so far on this subject are retrospective and devoid of definite diagnostic algorithms. In the retrospective studies of incidental thyroid involvement, the final diagnosis has been reached in only 30% to 50% of cases (5-7). There are considerable limitations in systematic reviews on this subject, such as publishing bias and significant heterogeneity in studies (8).

We conducted this retrospective study to detect the rate of incidental involvement in the thyroid gland in ^{18}F-FDG PET/computed tomography (CT) examination in our clinic and to determine the rate of malignancy among these patients.

METHODS

Patients

In our study, 9,974 patients who underwent ^{18}F-FDG PET/CT imaging between January 2015 and December 2016 with indications other than thyroid diseases in the Nuclear Medicine Department of Okmeydani Training and Research Hospital were evaluated, and 50 patients with definitive histopathological diagnosis of incidental thyroid nodules were included in the study. Patients showing focal or diffuse FDG uptake in the thyroid gland in the ^{18}F-FDG PET/CT study were evaluated and recorded as incidental involvement. Age, gender, ^{18}F-FDG PET/CT imaging indication, ^{18}F-FDG involvement (focal or diffuse), lesions' maximum standard uptake value (SUV_{max}), and histopathology of those who underwent surgery or fine-needle aspiration biopsy (FNAB) were recorded. The histopathological diagnoses of patients who underwent FNAB were categorized as malignant, benign, and suspicious. Histopathological diagnoses of patients who underwent thyroidectomy and FNAB were examined and compared with ^{18}F-FDG PET/CT findings. The cases with FNAB results that were inadequate, uncertain, and suspicious for malignancy (unless confirmed by total thyroidectomy) were excluded from the study. The incidence of incidental thyroid lesions, malignancy potentials of these lesions, the correlation of SUV_{max} and ^{18}F-FDG uptake patterns of lesions, with histopathological results of patients who underwent ^{18}F-FDG PET/CT study were examined. A retrospective evaluation was made by obtaining ^{18}F-FDG PET/CT imaging results from the archive in the nuclear medicine department and histopathological results from the patient files and pathology archive. This retrospective study was conducted with the approval of the Medical Ethics Committee of Okmeydani Training and Research Hospital, with the decision dated March 14, 2018, and numbered 615. Informed consent was obtained from all individual participants included in the study.

Imaging

PET/CT imaging of patients included in the study was done with a Siemens Biograph 6 LSO HI-RES integrated PET/CT device (Siemens Medical Solutions, Knoxville, TN, USA). After four to six hours of fasting, patients waited in a quiet and dark room just before their exam. Blood glucose was measured with a glucometer just before the radiopharmaceutical injection. All patients used an oral contrast agent before imaging. Patients with blood glucose levels below 150 mg/dL were injected intravenously with 0.15-0.20 mCi/kg ^{18}F-FDG. After a 60-minute waiting period, the patient's bladder was emptied, and the patient was placed in the supine position on the bed of the PET/CT scanner. First guideline topogram CT images were acquired, then subsequent PET images of body parts from the vertex to the proximal thigh were acquired. The images of the patients were completed in approximately 20 to 25 minutes, with an average of 7 to 8 bed positions. The CT portion of the PET/CT study was non-diagnostic and used for attenuation correction and anatomical localization of ^{18}F-FDG PET images.

Histopathological Evaluation

The biological material obtained while performing the diagnostic and treatment procedures (FNAB or thyroidectomy) was examined histopathologically in our hospital's pathology department, and immunohistopathological staining was performed as necessary.

Statistical Analysis

IBM SPSS Statistics 22 for statistical analysis (SPSS IBM, Turkey) program was used to evaluate the findings of the study. The appropriateness of the parameters to normal distribution was evaluated with the Shapiro-Wilk test. In addition to descriptive statistical methods (mean, standard deviation, frequency), in the comparison of quantitative data, Student's t-test was used for comparing the parameters that showed normal distribution, and the Mann-Whitney U test was used for parameters that did not show normal distribution. Fisher's exact test was used to compare qualitative data. Significance was evaluated at the level of $p<0.05$.

RESULTS

Incidental involvement in the thyroid gland was observed in 401 (4%) of patients who underwent ^{18}F-FDG PET/CT (focal 2.3%, diffuse 1.6%). Diffuse involvement was observed in 162 (41%) (Figure 1) and focal uptake in 239 (59%) of these patients. Histopathological diagnosis was obtained by FNAB in 43 patients, and surgery in 7 patients. The average patient

age was 60.84±13.01 (34-86) years. Ten (20%) were male, and 40 (80%) were female. Our study parameters included were SUV_{max}, histopathological diagnosis and incidental lesion tumor size (Table 1). SUV_{max} range from 2.73 to 29.27 with an average of 8.39±5.83. The average SUV_{max} for benign and malignant lesions were 7.56±3.81 (mean, 6.15) and 11.72±10.34 (mean, 7.18).

Tumor sizes ranged from 6 to 43 mm, and the average size was 19.47±9.27 mm. The size of the nodules, either malignant or benign, was ≤15 mm in 23 cases (46%) and ≥15 mm in 27 cases (54%). While 40 (80%) of 50 cases were diagnosed as benign, (Figure 2) 10 (20%) were diagnosed as malignant (Figure 3). When the size assessment was made in malignant cases, 6 of 10 were 15 mm and below. Although the malignancy rate was higher in nodules smaller than 15 mm, it was statistically insignificant. In benign nodules, 17 of 40 cases had a size of 15 mm or less.

Six out of 23 nodules (26%) smaller than 15 mm were found to be malignant. This finding was higher than the malignancy rate in all ^{18}F-FDG positive nodules (20%) but was not statistically significant. The average SUV_{max} were higher in the malignant group, but there was no statistically significant difference regarding SUV_{max} ($p>0.05$). Since there was no statistically significant difference between the SUV_{max} averages of malignant and benign nodules, a cut-off point could not be calculated.

DISCUSSION

Incidence of detecting thyroid nodules on the neck ultrasonography (USG) performed for a purpose other than the thyroid gland is between 14% and 46% (1). The nodule detection rate varies among different radiological imaging methods.

Table 1. SUV_{max}, nodule size, age, and gender distribution in benign and malignant nodule groups

	Diagnosis		p
	Benign	Malignant	
SUV_{max} Avg. ± SD (median)	7.56±3.81 (6.15)	11.72±10.34 (7.18)	[1]**0.689**
Tumor size (n, %)			
≤15 mm	17 (42.5%)	6 (60%)	[2]**0.480**
>15 mm	23 (57.5%)	4 (40%)	
Age mean ± SD	61.9±12.59	56.6±14.49	[3]**0.253**
Sex (n, %)			
Male	8 (20%)	2 (20%)	[2]**1.000**
Female	32 (80%)	8 (80%)	

[1]Mann-Whitney U test, [2]Fisher's exact test, [3]Student's t-test, SUV_{max}: Maximum standard uptake value, Avg.: Average, SD: Standard deviation

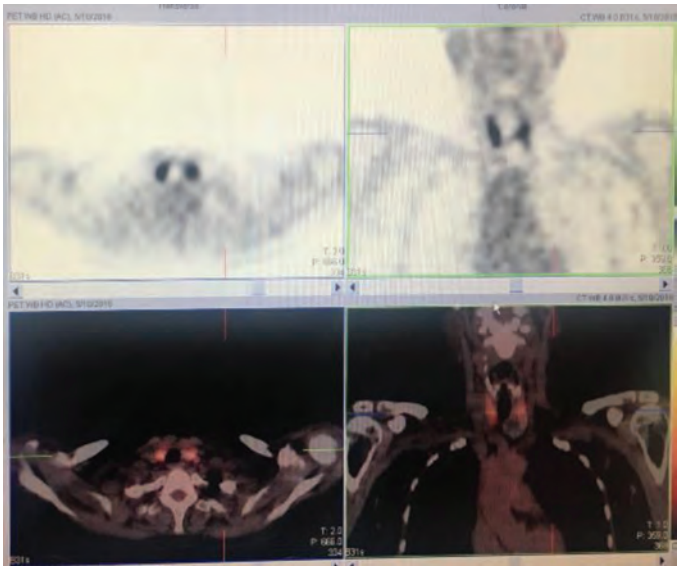

Figure 1. Chronic thyroiditis pattern showing diffuse FDG uptake. A 56-year-old female patient underwent ^{18}F-FDG PET/CT for restaging of cervical cancer. Axial PET and fusion images (left column) and coronal PET and fusion images (right column) show incidental diffuse FDG uptake in the thyroid gland (SUV_{max}: 14.69). The patient underwent FNAB, and her histopathology revealed lymphocytic thyroiditis

^{18}F-FDG: ^{18}Fluoro-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standard uptake value, FNAB: Fine-needle aspiration biopsy

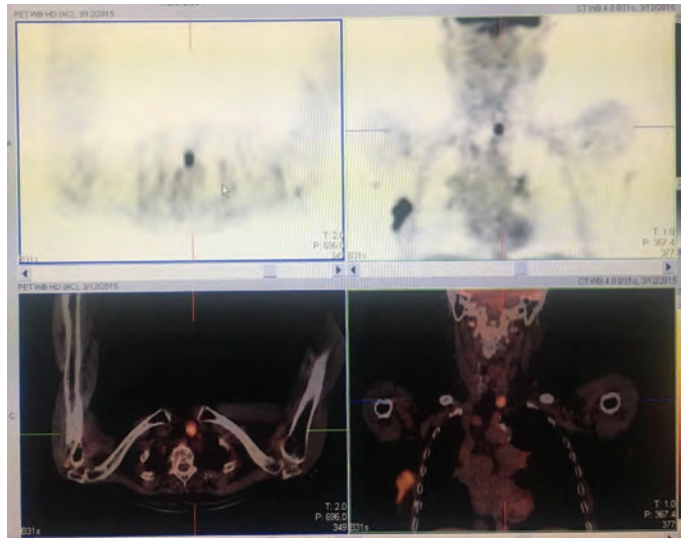

Figure 2. Benign thyroid nodule that shows focal FDG uptake. An 86-year-old female patient underwent an ^{18}F-FDG PET/CT study for the evaluation of cancer of unknown primary origin. Axial PET and fusion images (left column) and coronal PET and fusion images (right column) show focal FDG uptake in the left lobe of the thyroid gland. (SUV_{max}: 12.91). Correlation with USG showed a 15 mm nodule, and the FNAB results from this nodule were benign

^{18}F-FDG: ^{18}Fluoro-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standard uptake value, FNAB: Fine-needle aspiration biopsy, USG: Ultrasonography

Thyroid gland incidentalomas are seen in 16% of CT and magnetic resonance imaging studies and 27% of neck ultrasonographies (9,10). In an autopsy series, incidental nodules were more common in the thyroid gland. Mortensen et al. (11) reported that macroscopically at least one nodule was observed in half of the patients, and nodules were larger than 2 cm in approximately 33% of all cases.

The incidental detection rate of ^{18}F-FDG avid thyroid nodules in ^{18}F-FDG PET/CT studies has been reported between 0.1% and 4.3% (12). In our retrospective study, incidental uptake in the thyroid gland, either focal or diffuse, was observed in 401 (4%) of 9,974 patients who underwent ^{18}F-FDG PET/CT for evaluation of different malignancies. It is known that thyroid nodules are more common in women than in men. Also, ^{18}F-FDG PET/CT incidentalomas are more common in women (1). In our cohort, 74% of incidentalomas were detected in women. The nodule observed in the focal involvement area located incidentally in the thyroid gland is likely to be malignant. Therefore, the presence of nodules that show focal ^{18}F-FDG uptake should be evaluated with USG, and FNAB should be performed if necessary (13).

In our study, 60 of 239 patients with focal involvement underwent FNAB, and seven of them had a total thyroidectomy in addition to FNAB. Malignancy was detected in ten of the patients with malignancy-compatible cytology after total thyroidectomy and/or FNAB and was used as the gold standard to diagnose thyroid cancer. The risk of malignancy was calculated as 20% (10/50) for patients without FNAB. Inadequate and uncertain FNAB results and suspected malignant cases of FNAB (unless confirmed by total thyroidectomy) were excluded from the study. In a systematic review on this subject, the malignancy rates obtained with total thyroidectomy and FNAB in patients with incidental focal ^{18}F-FDG involvement in the thyroid gland were reported as 29.3%-33.2% (8). Bae et al. (7) reported the malignancy rate as 30.9% in patients with focal ^{18}F-FDG involvement in the thyroid gland. These rates are somewhat higher than the rates we found (20%). The probable reason for obtaining a rate below those cited in the literature is the low number of patients who had FNAB or total thyroidectomy, which is also a limitation of the study. However, cancer rates of focal incidentalomas were higher and were from 41.7% to 47% in some studies. However, these studies were limited and included a low number of patients in the study and made the histopathological diagnosis mostly by FNAB instead of an operation (14,15). Chen et al. (16) reported the malignancy rate of the ^{18}F-FDG positive thyroid nodules as 14%, a rate lower than that found in the literature. We think that the low risk of malignancy in this study may be due to bias in the evaluation of FNAB results on focal incidentalomas. In addition, geographical differences in which the study was conducted may be cause discordant malignancy risk.

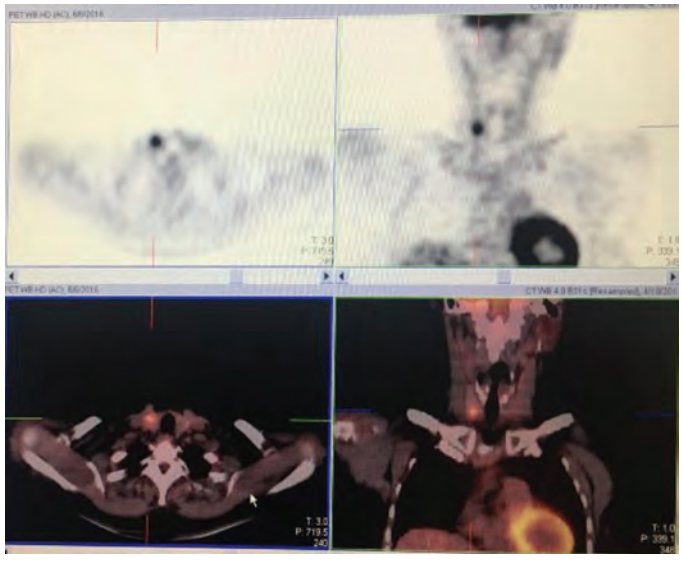

Figure 3. Malignant thyroid nodule that shows focal FDG uptake. A 46-year-old female patient underwent an ^{18}F-FDG PET/CT study for the evaluation of cancer of unknown primary origin. Axial PET and fusion images (left column) and coronal PET and fusion images (right column) show focal FDG uptake in the right lobe of the thyroid gland. (SUV_{max}: 7.8). Ultrasonography showed an 11 mm nodule corresponding to the focal uptake. FNAB from the nodule revealed atypia of unknown significance. Subsequently, the patient underwent a total thyroidectomy, and the pathology results revealed papillary thyroid carcinoma

^{18}F-FDG: ^{18}Fluoro-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standard uptake value, FNAB: Fine-needle aspiration biopsy

Determining a specific SUV_{max} cut-off value for the discrimination of benign and malignant thyroid nodules is another concern. Makis and Ciarallo (12) reported a statistically significant difference between the median SUV_{max} of benign thyroid incidentalomas (SUV_{max}: 4.8) vs malignant (SUV_{max}: 6.3). However, due to the wide range of overlap between the two groups, the authors did not find it reliable to determine the malignancy with this SUV_{max} threshold value. Pagano et al. (17) stated that malignant lesions have a higher SUV_{max} than benign lesions, and this has a positive correlation when SUV_{max}: >5. The meta-analyses also reported a significant difference between SUV_{max} of benign lesions and malignant lesions. However, no particular SUV_{max} cut-off value was identified because of the overlap between the two groups (4,8,18). In our study, the average SUV_{max} was higher in the group diagnosed as malignant. Still, the difference between benign and malignant nodules regarding SUV_{max} averages was not statistically significant ($p>0.05$).

In a study conducted by Shi et al. (19) with 5,216 patients, the malignant thyroid incidentalomas were significantly larger than benign lesions (malignant 1.8±0.8 cm, benign 1.3±0.5 cm, p=0.006). They had higher SUV_{max} (11.3 vs. 4.8, p<0.001). We chose a 1.5 cm cut-off value arbitrarily. There was no statistically significant difference regarding the distribution rates between the tumor size groups (p>0.05).

The 2015 American Thyroid Association (ATA) guideline suggests that if the uptake is diffuse, it is confirmed by USG or clinical findings regarding the ^{18}F-FDG involvement in the thyroid gland. There is no need for further imaging examination (strong recommendation medium level of evidence). In focal ^{18}F-FDG uptake, if the nodule is confirmed with USG and the size of the nodule is >1 cm, thyroid FNAB is recommended because the risk of malignancy increases (strong advice medium evidence) (20). Similarly, the 2016 Agency for Care Effectiveness (ACE) guideline recommends FNAB for increased risk of malignancy in thyroid nodules that show focal ^{18}F-FDG uptake on PET. However, if the involvement is diffuse, they do not recommend further investigation. Unlike the ATA guideline, the ACE guideline does not make any recommendations regarding the nodule size for performing a biopsy of the nodule that shows ^{18}F-FDG uptake (21).

CONCLUSION

Thyroid incidentaloma was detected in 4% of patients who underwent ^{18}F-FDG PET/CT for non-thyroid cancer. The pattern of FDG uptake in these patients was focal in 59% and diffuse in 41%. Thyroid malignancy was detected in 20% of patients with ^{18}F-FDG PET/CT with focal FDG uptake. There was no significant difference between the groups diagnosed benign and malignant concerning SUV_{max} and lesion size. The cut-off value for SUV_{max} could not be calculated because there was no relationship between SUV_{max} and malignancy.

It was thought that thyroid incidentalomas that show focal ^{18}F-FDG uptake on ^{18}F-FDG PET/CT studies should be correlated with USG. Because of the high risk of malignancy, analysis of histopathologies should be performed with FNAB.

Ethics

Ethics Committee Approval: This retrospective study was conducted with the approval of the Medical Ethics Committee of Okmeydani Training and Research Hospital, with the decision dated March 14, 2018, and numbered 615.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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Authorship Contributions

Surgical and Medical Practices: İ.F.C., Concept: İ.F.C., T.Ö., Design: İ.F.C., T.Ö., Data Collection or Processing: İ.F.C., Analysis or Interpretation: İ.F.C., T.Ö., Literature Search: İ.F.C., Writing: İ.F.C., F.Ö., S.S.K.

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ORIGINAL ARTICLE

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Frequency and Clinical Significance of Appendectomy and Tonsillectomy in Patients with Inflammatory Bowel Disease

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Abstract

Objective: Appendectomy and tonsillectomy remain controversial environmental factors in the etiology of inflammatory bowel disease (IBD). In this study, we aimed to investigate the frequency of tonsillectomy and appendectomy in patients with IBD. In addition, the effects of tonsillectomy and appendectomy on age of IBD diagnosis, site of intestinal involvement, and medical treatments were investigated.

Methods: A total of 131 IBD patients and 76 healthy controls (HCs) were included in this study. All of these patients included in this study were asked if they had undergone an appendectomy or tonsillectomy and their age at the time of the surgery. The age of diagnosis of IBD, medical treatment, disease location, and perianal involvement characteristics of the patients collected from the hospital records were evaluated.

Results: Of 90 patients with ulcerative colitis (UC), 2 patients underwent appendectomy after the age of 20 and after the diagnosis of UC. Compared with HCs, appendectomy and the age during operation were not associated with the incidence of UC. Moreover, 8 of 41 patients with Crohn's disease (CD) had undergone appendectomy. Of these, 6 patients had undergone surgery before the age of 20 and before the diagnosis of CD. Compared with HCs, appendectomy and the operative age were significantly associated with the incidence of CD. No significant relationship was observed between the groups in terms of tonsillectomy.

Conclusion: Appendectomy was associated with an increased risk of developing CD; however, no effect was observed on the risk of developing UC. Moreover, tonsillectomy was not associated with an increased risk of incidence of both CD and UC.

Keywords: Inflammatory bowel disease, appendectomy, tonsillectomy

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal system that occurs with periods of activity and remission. Ulcerative colitis (UC) and Crohn's disease (CD) are the 2 main forms of IBD and separate from each other by their endoscopic and pathological findings (1). The etiopathogenesis of IBD is multifactorial and has not yet been fully understood. However, it is believed that genetic and environmental factors trigger the disease (2). Environmental factors and those affecting the microbiota are held responsible for the occurrence of the disease in people with a genetic predisposition (3). Considering the close relationship of the intestinal content with the mucosal immune system, the microbiota appears to be the most important environmental risk factor for IBD.

The tonsils, appendix, and Peyer's patches are the most important components of the mucosa-associated lymphoid tissue. Therefore, appendectomy and tonsillectomy are among the main environmental factors that affect the structure of the intestinal bacteria (4). Appendectomy and tonsillectomy, namely MALTectomy, can cause changes in intestinal immunity (5,6). MALTectomy and the resulting immune changes have been associated with IBD and many diseases with autoimmune components and end-organ inflammation (7,8). The results of

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studies investigating the relationship between appendectomy, tonsillectomy, and IBD are contradictory (6,9,10).

Smoking and appendectomy are among the most important environmental risk factors identified for IBD (11). Moreover, the risk of appendectomy was reported to be increased among children whose parents have smoking habit (12). This finding further complicates the relationship between smoking, appendectomy, and IBD.

In our study, we investigated the prevalence of tonsillectomy and appendectomy, which is thought to cause changes in the intestinal microbiome and affect intestinal mucosal immunity in UC and CD patients. In addition, we evaluated the effects of tonsillectomy and appendectomy and the age during operation on age of IBD diagnosis, disease location, and medical treatment. We also investigated the relationship of smoking with appendectomy and tonsillectomy in IBD patients.

METHODS

This study protocol conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the University of Health Sciences, University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital (number: E-48670771-514.10, date: 26.01.2021). Informed consent was obtained from all participants of this study for analysis and publication of their data for scientific purposes.

In total, 131 IBD patients, including 90 patients with UC and 41 patients with CD, who were followed-up from the gastroenterology clinic and whose diagnosis of IBD was definite endoscopically, pathologically, and radiologically, were enrolled in the study. Patients <18 years of age, patients with incomplete information in their patient files and incomplete answers to questions, and patients with an uncertain diagnosis of IBD were excluded from the study. Healthy controls (HCs) who were matched in terms of age and gender were also included in the study. People who applied to the hospital for their routine check-up and had no known diseases, malignancy, or drug history were selected to be part of the HCs group.

The IBD patients and the HCs participants were asked about the history of appendectomy or tonsillectomy, their age at the time of surgery, their smoking habits, and the smoking status of their parents to understand their general nicotine exposure.

In this study, we collected data on the age of diagnosis of IBD, medical treatment, disease location, and perianal involvement characteristics of patients from the hospital records and evaluated them. Patients with UC were grouped as proctitis, distal colitis, left-sided colitis, and pancolitis according to the disease site. Patients with CD were grouped as ileal, colonic, and ileocolonic.

Statistical Analysis

The compatibility of numerical variables to normal distribution was tested using the Shapiro-Wilk test. The Mann-Whitney U test was used for comparing numerical variables that were not normally distributed in two groups, and the Kruskal-Wallis test was used for comparison of three groups. Relationships between categorical variables were tested using the chi-squared test. The risk of developing CD in those who underwent appendectomy was calculated using odds ratio (OR). IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) was the software used for the statistical analyses. The p value <0.05 was considered significant.

RESULTS

The study included 90 patients (45 male, 50%) with UC, 41 patients (27 male, 65.9%) with CD, and 76 HCs (37 male, 48.7%). The median age of UC patients was 38 [interquartile range (IQR): 30-51] years, CD patients was 40 (IQR: 35-45) years, and the HCs was 37 (IQR: 29-47) years. No significant difference was observed between the groups in terms of age, gender, body mass index, family history of IBD, and smoking status ($p>0.05$). In addition, no relationship was found between nicotine exposure in IBD patients (due to smoking habits of their parents or of their own), appendectomy, and tonsillectomy. However, we observed that the appendectomy rate was higher in CD patients compared with that of UC patients and the HCs ($p=0.001$). Demographic and clinical characteristics of UC and CD patients and the HCs are shown in Table 1.

Appendectomy

In this study, 2 of 90 UC patients (2.2%) underwent appendectomy after the age of 20 and after the diagnosis of UC. Compared with the HCs, no association was observed between appendectomy and the age during surgery in patients with UC ($p=0.287$, $p=0.414$, respectively; Table 2). The mean (standard deviation) time from the diagnosis of UC to appendectomy was 8.5 (2.1) years. The mean follow-up period of the two patients who underwent appendectomy was 14.5 (0.7) years. No significant difference was observed between patients with UC who had undergone appendectomy and those who did not undergo appendectomy, in terms of drug use (corticosteroids, azathioprine/6-mercaptopurine, or anti-tumor necrosis factor agents) and disease location ($p>0.05$; Table 3, 4).

Furthermore, we found that appendectomy was performed in 8 (19.5%) of 41 patients with CD. Of these, 6 patients (75%) had undergone surgery before the age of 20 and before the diagnosis of CD. The mean time from appendectomy to the diagnosis of CD was 16 (13.3) years. The mean follow-up period of these patients after the diagnosis of CD was 5.8 (3.5) years. In terms of disease location and drug use, no significant difference was found between CD patients who had undergone appendectomy and those who did not undergo appendectomy (p>0.05). Compared with the HCs, appendectomy and operative age were significantly associated with the incidence of CD (p=0.019, both). The probability of developing CD was 4.3 times higher in patients with appendectomy (OR: 4.30, 95% CI: 1.20-15.31).

Table 1. Demographic and clinical characteristics of the patients and control groups

	UC (n=90)	CD (n=41)	Control (n=76)	p
Sex, n (%)				
Male	45 (50.0)	27 (65.9)	37 (48.7)	0.165
Female	45 (50.0)	14 (34.1)	39 (51.3)	-
Age, median (IQR)	38.0 (30.0-51.0)	40.0 (35.0-45.0)	37.0 (29.0-47.5)	0.840
BMI, median (IQR)	24.7 (22.0-27.2)	25.4 (23.8-27.2)	24.0 (22.0-27.0)	0.302
Smoker	30 (33.3)	18 (43.9)	31 (40.8)	0.431
Family history	7 (21.9)	0 (0.0)	-	0.132
Disease onset age median (IQR)	32.0 (25.0-43.0)	32.0 (28.0-39.0)	-	0.800
Appendectomy, n (%)				
Yes	2 (2.2)	8 (19.5)	4 (5.3)	0.001*
No	88 (97.8)	33 (80.5)	71 (94.7)	-
Tonsillectomy, n (%)				
Yes	7 (7.8)	2 (4.9)	5 (6.7)	0.828
No	83 (92.2)	39 (95.1)	70 (93.3)	-

*p<0.05, IQR: Interquartile range, UC: Ulcerative colitis, CD: Crohn's disease

Table 2. Age composition of UC and CD patients and the control group

	Appendectomy			Tonsillectomy		
Age (year)	<20	>20	p	<20	>20	p
UC, n (%)	0 (0.0)	2 (100)	0.414	6 (85.7)	1 (14.3)	0.398
Control, n (%)	0 (0.0)	4 (100)		5 (100)	0 (0.0)	
CD, n (%)	6 (75)	2 (25)	0.019*	0 (0.0)	2 (100)	0.014*
Control, n (%)	0 (0.0)	4 (100)		5 (100)	0 (0.0)	

*p<0.05, UC: Ulcerative colitis, CD: Crohn's disease

Table 3. Effects of appendectomy and tonsillectomy on anti-TNF needs in UC and CD patients

	Appendectomy			Tonsillectomy		
	Yes	No	p	Yes	No	p
UC, anti-TNF, n (%)						
Yes	0 (0.0)	9 (10.2)	0.514	1 (14.3)	8 (9.6)	0.708
No	2 (100)	79 (89.8)		6 (85.7)	75 (90.4)	
CD, anti-TNF, n (%)						
Yes	4 (50)	12 (36.4)	0.482	1 (50)	15 (38.5)	0.748
No	4 (50)	21 (63.6)		1 (50)	24 (61.5)	

TNF: Tumor necrosis factor, UC: Ulcerative colitis, CD: Crohn's disease

Tonsillectomy

Results of this study stated that 7 (7.8%) patients with UC, 2 (4.9%) patients with CD, and 5 (6.7%) patients in the HCs had undergone tonsillectomy. No significant difference was observed among the groups in terms of tonsillectomy (p=0.828; Table 1). However, 2 patients with CD had tonsillectomy after the age of 20, and it was a significant difference compared with the HCs (p=0.014; Table 2). In IBD patients, the relationship between tonsillectomy and the onset time and location of the disease was not significant (p>0.05; Table 5).

Table 4. Appendectomy vs. no appendectomy in UC and CD patients

	Appendectomy		p
	Yes	No	
UC, n (%)	2 (2.2)	88 (97.8)	-
Disease onset age, median (IQR)	46.5 (38.0-55.0)	32.0 (25.0-42.0)	0.136
Smoker, n (%)	0 (0.0)	30 (34.1)	0.200
Location, n (%)			
Proctitis	0 (0.0)	12 (13.6)	0.563
Distal colitis	0 (0.0)	20 (22.7)	
Left-sided colitis	1 (50.0)	18 (20.5)	
Pancolitis	1 (50.0)	38 (43.2)	
CD, n (%)	8 (19.5)	33 (80.5)	-
Disease onset age, median (IQR)	35.0 (20.5-43.0)	32.0 (29.0-38.0)	0.834
Smoker, n (%)	4 (50.0)	14 (42.4)	0.699
Location, n (%)			
Ileum	3 (37.5)	14 (43.8)	0.429
Colon	0 (0.0)	3 (9.4)	
Ileocolon	5 (62.5)	15 (46.9)	

UC: Ulcerative colitis, CD: Crohn's disease, IQR: Interquartile range

Table 5. Tonsillectomy vs. no tonsillectomy in UC and CD patients

	Tonsillectomy		p
	Yes	No	
UC, n (%)	7 (7.8)	83 (92.2)	
Disease onset age, median (IQR)	38.0 (22.0-46.0)	32.0 (25.0-43.0)	0.619
Smoker, n (%)	1 (14.3)	29 (34.9)	0.234
Location, n (%)			-
Proctitis	0 (0.0)	12 (14.5)	0.464
Distal colitis	2 (28.6)	18 (21.7)	
Left-sided colitis	1 (14.3)	18 (21.7)	
Pancolitis	4 (57.1)	35 (42.2)	
CD, n (%)	2 (4.9)	39 (95.1)	-
Disease onset age, median (IQR)	33.0 (32.0-34.0)	32.0 (25.0-39.0)	0.927
Smoker, n (%)	2 (100.0)	16 (41.0)	0.064
Location, n (%)			
Ileum	2 (100.0)	15 (39.5)	0.168
Colon	0 (0.0)	3 (7.9)	
Ileocolon	0 (0.0)	20 (52.6)	

UC: Ulcerative colitis, CD: Crohn's disease, IQR: Interquartile range

DISCUSSION

The relationship between appendectomy and IBD is considered complex. The appendix contains dense structures of lymphoid tissue, such as Peyer's patches. It is the most important region where immunoglobulin A is produced, which is very important for regulating the density and quality of the intestinal flora. Considering its shape and location, the appendix is also home for commensal bacteria in the body. Moreover, the appendix is of great importance as a microbiota reservoir (13). While some studies report an increased risk of CD after appendectomy, there are studies reporting otherwise (5,10,14,15). A study reporting that appendectomy affected the risk of developing CD based on age, gender, and operative diagnosis (perforated or non-perforated) also stated that appendectomy performed before the age of 10 reduced the risk of onset of CD (10).

Another study reported that appendectomy performed at pediatric age did not pose a potential risk for incidence of pediatric CD. It also stated that undiagnosed early symptoms of CD could be confused with appendicitis symptoms (16). The impact of appendectomy on the clinical course of CD is still controversial. Contrary to a few studies reporting no risk, appendectomy has been reported to increase surgical risk in CD patients (17,18). Andersson et al. (10) reported that the increased surgical risk for CD was observed only in patients operated for perforated appendicitis. Furthermore, an increased risk of intestinal resection has been reported in CD patients with a history of appendectomy after perforated appendicitis (10,14).

Cosnes et al. (19) reported that CD patients with a history of appendectomy were associated with more proximal disease, greater risk of stenosis, and lesser anal fistula; however, appendectomy did not affect the severity of the disease. In addition, it was emphasized that immunosuppressant, immunomodulatory, and anti-tumor necrosis factor requirements are not affected by appendectomy independent of the localization of the disease. It is claimed that appendectomy and CD share common genetic and environmental characteristics, and appendectomy alone does not show any immunomodulatory effect (19).

In our study, history of appendectomy was higher in CD patients than in the control group. We found that appendectomy increased the risk of developing CD by 4.3 times. Therefore, appendectomy is an increased risk factor for patients with CD. In this study, appendectomy was performed in 75% of patients before the age of 20, and a diagnosis of CD was made at a mean time of 16 (13.3) years after appendectomy. Unlike our study, Kurina et al. (20) reported that appendectomy performed after the age of 20 was associated with an increased risk of CD that will develop later. However, this risk was limited to those diagnosed with CD within an average of 1 year after appendectomy.

In our study, intestinal resection was not investigated in CD patients; however, no relationship was found between appendectomy and perianal disease, which is one of the poor prognostic factors for CD. In addition, the history of appendectomy had no effect on the age at diagnosis of CD, site of intestinal involvement of the disease, and medical treatment. However, ileum involvement of 42.8% and ileocolonic involvement of 57% was observed in all of the patients with appendectomy.

Many studies have claimed that the appendix has a physiological role in regulating the immunological response to the intestinal microflora and appendectomy reduces the risk of developing UC (21). A study investigating the relationship of appendectomy with incidence of UC, including only the patients with extensive and severe colitis, emphasized that appendectomy has a protective effect in UC patients. In other words, the study reported that the protective effect of appendectomy can only be explained for pancolitis and severe colitis (22). In the present study, we included all patients with left colon, distal, and rectal involvement in addition to pancolitis. We found no difference in disease location and medical treatment between UC patients who had undergone appendectomy and those who did not undergo appendectomy.

Many studies reported that performing appendectomy in childhood and adolescence causes a decrease in the risk of developing UC; however, the same effect is not valid for appendectomy in adults (10,22). These findings suggest the presence of age-dependent differences in the pathogenesis of appendicitis. In addition, patients who underwent appendectomy before the diagnosis of UC have reduced risk of UC-related hospitalizations and colectomy (23). In our study, only two patients with UC had a history of appendectomy. Moreover, in both the patients, appendectomy was performed after the age of 20. Interpretation of the age of appendectomy in terms of the risk of development of UC was not possible because of the small number of patients included in this study.

The etiological relationship between tonsillectomy and incidence of both CD and UC remains unclear. Some studies have reported that performing tonsillectomy before the diagnosis of IBD does not have any relationship with the risk of onset of both UC and CD (20,24). In another study, no significant relationship was found between tonsillectomy and IBD (25). Another study showed that tonsillectomy was associated with an increased risk of developing CD; however, this relationship was not found in

case of onset of UC (6). Similar to a study that reported ileum as the most common disease site in CD patients who had previously undergone tonsillectomy, in our study, ileum was involved in 2 CD patients who had previously undergone tonsillectomy (26).

Study Limitations

This study has few limitations. First, the effects of appendectomy and tonsillectomy on surgical history and disease activities associated with IBD could not be evaluated. In addition, inclusion of less number of patients who underwent appendectomy and tonsillectomy limits our research results on IBD disease location and treatment effect of these operations.

CONCLUSION

Findings of this study showed that appendectomy is associated with an increased risk of onset of CD, as an indication that appendectomy and CD have similar environmental or genetic characteristics. However, no effect of appendectomy could be observed on age at diagnosis, location of the disease, and medical treatment of UC and CD. We have shown that appendectomy does not increase the risk of developing UC. Furthermore, tonsillectomy is not associated with an increased risk of developing CD or UC.

Ethics

Ethics Committee Approval: Ethics Committee of the University of Health Sciences, University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital (number: E-48670771-514.10, date: 26.01.2021).

Informed Consent: Informed consent was obtained from all participants of this study for analysis and publication of their data for scientific purposes.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.G., D.Ö.K., Design: Y.G., D.Ö.K., Data Collection or Processing: Y.G., D.Ö.K., Analysis or Interpretation: Y.G., D.Ö.K., Literature Search: Y.G., D.Ö.K., Writing: Y.G., D.Ö.K.

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CASE REPORT

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Extracorporeal Membrane Oxygenation Support on Acute Fulminant Myocarditis Associated with Parainfluenza Infection: A Case Report

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Abstract

Acute fulminant myocarditis (AFM) is a clinical condition that can lead to sudden onset of rapidly progressing cardiogenic shock with significant arrhythmia and possible cardiac arrest. Mechanical circulation support has been reported to provide effective cardiac support in patients with AFM. In this article, we aimed to present the case of a 14-year-old girl with AFM who experienced a cardiogenic shock and resistant ventricular tachycardia unresponsive to medical treatment; however, she could be successfully treated with veno-arterial extracorporeal membrane oxygenation and discharged without neurological sequelae from the hospital.

Keywords: Extracorporeal membrane oxygenation, cardiogenic shock, myocarditis, parainfluenza, ventricular tachycardia

INTRODUCTION

Acute fulminant myocarditis (AFM) is a clinical condition that can lead to sudden onset of rapidly progressing cardiogenic shock with significant arrhythmia and possible cardiac arrest. In patients with AFM who are unresponsive to medical treatment, mechanical circulation support can provide effective cardiopulmonary support (1-3).

In this article, we have presented the case of a 14-year-old girl with AFM who experienced cardiogenic shock and resistant ventricular tachycardia (VT) unresponsive to medical treatment, which was successfully treated with veno-arterial (VA) extracorporeal membrane oxygenation (ECMO).

CASE PRESENTATION

A previously healthy 14-year-old girl was admitted to the emergency service with the complaint of upper respiratory tract infection for a week. She then developed complaints of shortness of breath, fatigue, cough, and palpitations the next day. On physical examination, the patient's general condition seemed poor. She showed dyspnea and tachypnea, and had 87% oxygen saturation, 40/min respiratory rate, 190-bpm heart rate, and 90/50 mmHg blood pressure, with subcostal and intercostal retractions. On auscultation, bilateral breath sounds were decreased in the lower zones and extensive crepitation rales were present. On posterio-anterior chest X-ray, bilateral blunting of the costophrenic and cardiophrenic angles as well as paracardiac infiltrationwas observed (Figure 1).

The patient's blood test examination results were as follows: White blood cells: 13,700/µL, hemoglobin level: 11.7 g/dL, platelet count: 133,000/µL, sodium level: 130 mmol/L, potassium level: 4.8 mmol/L, calcium: 8.2 mg/dL, lactate dehydrogenase: 878 U/L, aspartate aminotransferase (AST): 471 U/L, alanine aminotransferase (ALT): 696 U/L, C-reactive protein: 9.1 mg/L, urea: 46 mg/dL, creatinine level: 0.76 mg/dL, prothrombin time: 25.9 s (9.6-14.1), activated partial thromboplastin time:

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33.4 s (19-33), international normalized ratio: 2.32 (0.8-1.2), in the venous blood gas pH: 7.42, pCO_2: 33.5, HCO_3: 21.4, base excess: 2.29, lactate level: 1.6 mmol/L (the values between brackets refer to normal ranges). The patient was admitted with the diagnosis of pneumonia and pleural effusion. Due to complaints of chest pain and hypoxemia and VT observed in electrocardiography (Figure 2), the patient was transferred to the pediatric intensive care unit (PICU). Consent was obtained from the patient.

Transthoracic echocardiography (TTE) demonstrated large heart cavities in the left portion (left ventricular end-diastolic diameter: 54 mm), decreased systolic ejection fraction [(EF) 34%], and moderate insufficiency in the mitral valve (Figure 3).

The patient's condition was considered as AFM because of the rapid deterioration. Amiodarone was intravenously (IV) administered with a loading dose of 5 mg/kg twice for VT. However, due to continued VT, lidocaine (1 mg/kg/10 min) was administered as a loading dose and 25 µg/kg/min IV infusion as a mainteinance dose. The blood test results revealed creatine kinase myocardial band level of 6.5 U/L (0.6-6.3) and troponin level of 0.87 ng/mL (0.01-0.04).

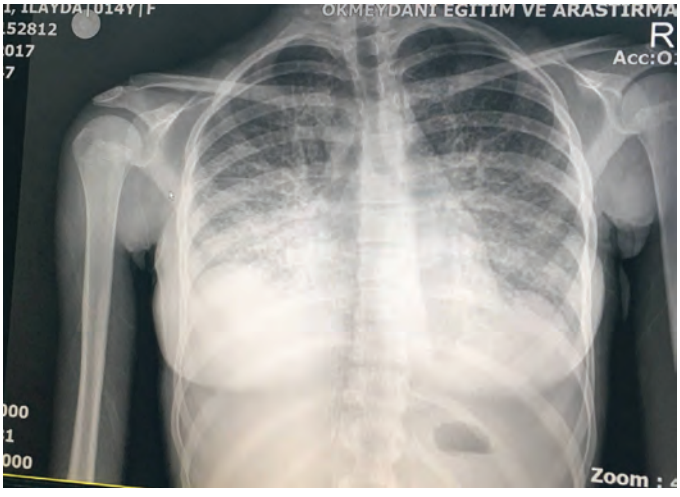

Figure 1. Patient's chest X-Ray

After 12 h of admission to the PICU, the patient's blood tests were repeated, and the results were as follows: AST: 1,803 U/L, ALT: 1,679 U/L, urea: 63 mg/dL, albumin: 0.61 g/dL, venous blood gas pH: 7.38, pCO_2: 30.1, HCO_3: 19.5, BE: -6.5, and lactate: 11.3. The patient was connected to a mechanical ventilator with endotracheal entubation, and due to hypoperfusion, IV milrinone (0.5 mcg/kg/min) and low-dose IV noradrenalin (0.06 mcg/kg/min) were initiated as inotropic therapy; amiodarone dose was increased to 15 mg/kg/day; and lidocaine dose was also increased to 50 mcg/kg/min for resistant VT. Meanwhile, 1 g/kg IV immunoglobulin, 1 g pulse steroid, and 1 g/kg of 20% human albumin were also adminsitered.

After 2 h, the patient's condition worsened. Systemic hypoperfusion (with metabolic acidosis, hypoxemia, and lactate elevation), hypotension (80/45 mmHg), and decreased EF in TTE (EF 10%) were observed. Because of the resistant cardiogenic shock and VT, the patient was connected to a VA-ECMO system. The cannulation sites were femoral artery with 18-F cannulae and jugular vein with 24-F cannulae. Then, the frequency of VT decreased. TTE was performed daily. EF was then gradually increased (on the 8th day of ECMO EF was 45%). VA-ECMO support was discontinued after 188 h. The tracheal aspirate sample was tested using multilocus polymerase chain reaction, and the sample was positive for parainfluenza virus. However, because of the hemodynamic stability and increased EF (to 45%), ribavirin was not administered. No complications were observed related to ECMO.

After the discontinuation of ECMO, VT was continued, and flecainide was administered instead of lidocaine, because of the 7-day maximum dose restriction. Beta blocker was also added to the regime. After 2 days, the patient was extubated, supported with a continuous positive airway pressure, and no additional oxygen was provided.

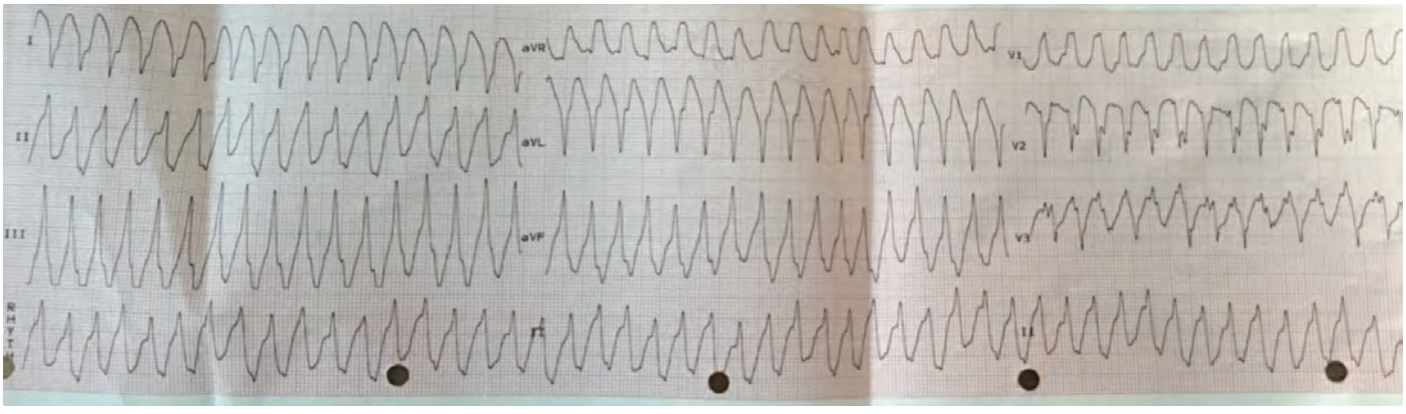

Figure 2. Patient's electrocardiogram with ventricular tachycardia

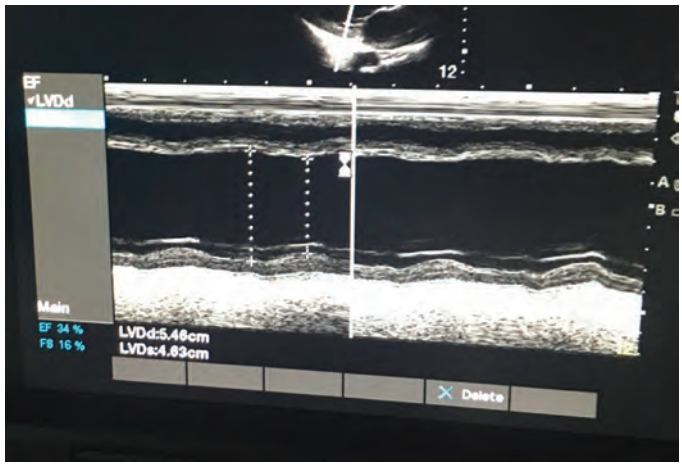

Figure 3. Patient's transthoracic echocardiogram

The frequency and duration of arrthymia was decreased gradually and finally stopped. TTE before discharging from the hospital revealed that the left heart cavities were enlarged (left ventricular end-diastolic volume: 54 mm), left ventricular EF was 47%, and moderate mitral regurgitation with central origin was present. The patient was discharged from the hospital with no neurological sequelae, and triple antiarrhythmic drugs, enalapril, and furosemide were prescribed.

DISCUSSION

The clinical condition of pediatric patients with AFM can worsen rapidly and unpredictably within hours of first presentation. AFM involves acute illness with hemodynamic derangement and ventricular arrhythmias due to a severe inflammatory process, and patients require the support of cardiac pump function and/or the urgent management of serious arrhythmias (4).

The selection of an appropriate therapy for ventricular arrhythmias focused on the prevention of sudden cardiac death and associated medical conditions. The management of arrhythmia may include appropriate antiarrhythmic therapy with drugs, implantable devices, ablation, or surgery. A beta blocker and amiodarone were recommended for recurrent polymorphic VT. IV lidocaine may be considered for the treatment of recurrent sustained VT or ventricular fibrillation (VF) in patients not responding to beta-blockers or amiodarone. Electrical cardioversion or defibrillation is recommended in patients with sustained and haemodynamically untolerated VT or VF. Urgent coronary angiography is indicated in these patients for revascularization when considering myocardial ischemia. Radiofrequency catheter ablation with the implantation of a left ventricular assist device/implantable cardioverter defibrillator should be considered in patients with recurrent VT or VF not responding to revascularization and optimal medical treatment. When the conventional therapy of medication, implantable devices, and ablation fails to convert refractory VT, leading to cardiogenic shock, ECMO can be performed for maintaining the hemodynamic stability and end-organ perfusion until further decision or recovery (5,6). In our case, ECMO was considered as the mechanical support for AFM because of sustained ventricular tachyarrythmia unresponsive to medical treatment and infeasible radiofrequency catheter ablation. However, the outcomes after ECMO for cardiac insufficiency in children are associated with underlying diseases (7). In a meta-analysis about the clinical outcomes in pediatric patients hospitalized with AFM and treated with ECMO, the survival rates were reported to be between 53.8% and 83.3% (8). Li et al. (9) reported the case of a 9-year-old girl with AFM, who rapidly worsened into pulseless VT and refractory cardiac arrest despite prolonged cardiopulmonary resuscitation for nearly 180 min and multiple antiarrhythmic therapy. They performed ECMO, and the girl recovered with intact cardiac and neurocognitive functions after 221 h of ECMO treatment. Similarly, in our report, after 188 hof ECMO treatment, our patient successfully recovered without cardiac and neurocognitive damage.

Recent reports with larger cohorts indicated that AFM is associated with overall worse outcomes that included lower left ventricular EF at the last follow-up, higher in-hospital mortality, and increased rates of cardiac transplantation (8-11). Mechanical circulation support can be considered at the first line of treatment. The disease has a high mortality unless provided with effective and on-time intervention with mechanical circulation support. The survival rate of patients with mechanical circulation support can rise up to 80%. Especially, in case of cardiogenic shock and resistant VT, mechanical circulation support is a good option for reducing the mortality rate and increasing the healing rate of myocardial muscles. As alternatives to mechanical circulation support, intra-aortic balloon pump, percutaneous cardiopulmonary support system, and ventricular assist device can be used. However, in children, ECMO is used more frequently because of its ease of use, low invasiveness, and more effective outcomes (3,12,13).

Viral infections are frequently the preliminary etiology of AFM. However, parainfluenza-related myocarditis has been less frequently reported (14,15). Parainfluenza virus was detected in the tracheal aspiration fluid of our patient. Ribavirin can be used as an antiviral agent (14-16). However, due to the fact that our patient's renal function was insufficient and EF increased to 40%,

ribavirin was not used. In addition, there are only limited studies available on the use of ribavirin in respiratory tract infections caused by parainfluenza virus. However, studies on whether IV immunoglobulin is effective or not has been reported in the past (15-17).

Our patient was administered pulse methylprednisolone with pentaglobulin. Corticosteroids reduce the amount of T lymphocytes, which are the mediators of ongoing heart damage in AFM through lysis. With a reduced number of T lymphocytes, cardiac ventricular function has been reported to improve (15-17).

CONCLUSION

Treatment of cardiogenic shock and resistant VT related to AFM should involve a multidisciplinary approach, such as mechanical circulation support, antiarrhythmic drugs, inotropic drugs, immunoglobulin, steroids, and other supportive treatments.

Ethics

Informed Consent: Consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.İ., F.A., Design: A.İ., F.A., Data Collection or Processing: M.A., F.A., Analysis or Interpretation: M.A., F.A., Literature Search: M.A., Writing: M.A.

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

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CASE REPORT

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Isolated Finding of Intermittent Compression of the Trochlear Nerve by a Dolichoectatic Basilar Artery

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Abstract

Vertebrobasilar dolichoectasia (VBD) is a rare disorder characterized by elongation and tortuosity of the vertebrobasilar arteries. Clinical manifestations can range from ischemic stroke and progressive compression of cranial nerves and brainstem to cerebral hemorrhage and hydrocephalus. Here, we report a case of intermittent diplopia complaint when looking down with a tilted head position for 3 months. His neuro-ophthalmic examination was within normal limits. Further, magnetic resonance and angiographic images revealed a dolichoectatic basilar artery compressing the right lateral brainstem. VBD treatment is controversial; there is still no effective treatment and only complications can be treated. Surgical options may be useful in very limited situations, but advances in stent technology are promising in the treatment of VBD. To our knowledge, no case in the literature describes intermittent trochlear nerve compression by VBD.

Keywords: Basilar artery, dolichoectasy, intermittent, ophthalmoplegia

INTRODUCTION

The term dolichoectasia is derived from "dolichos" and "ectasia", meaning elongation and dilatation (1). Vertebrobasilar dolichoectasia (VBD) is a rare disorder that is characterized by the elongation and tortuosity of the vertebrobasilar arteries affecting the neural elements and the brainstem (1), and it is commonly associated with the basilar artery (2). Based on the data obtained from the results of angiography and autopsy, the overall incidence of VBD is <0.05% but can differ among ethnic groups (1). VBD parameters are as follows: Basilar or vertebral artery diameter >4.5 mm, deviation of any portion of either artery >10 mm from the shortest expected course, or basilar and vertebral artery length >29.5 and >23.5 mm, respectively (2). Clinical manifestations of VBD include ischemic stroke, progressive compression of cranial nerves and brainstem, cerebral hemorrhage, and hydrocephalus. Midbrain symptoms are generally caused by ischemia or local compression (3). Ocular motor nerve paresis has been reported with recurrent trochlear nerve paresis being remarkably rare (3). Herein, we present an usual case of isolated trochlear nerve paresis associated with intermittent diplopia for just 30 seconds when looking down due to a dolichoectatic basilar artery.

CASE PRESENTATION

A 54-year-old man was admitted to our clinic complaining of intermittent diplopia for 3 months. He was tilting his head down for a few seconds when the vision problem started. He was on antihypertensive medication for 7 years, and his blood pressure had been within normal limits. He denied any other comorbidity. There was no history of trauma, headache, vertigo, or focal deficit.

During ophthalmological examination, visual acuity, color vision, pupil size, and reactivity were normal, and no ptosis, nystagmus, or eyelid twitch was observed. Fundus examination was bilaterally insignificant. Further, extraocular muscle functions

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were normal, but he complained about vertical diplopia while reading three to four times a day for a few seconds. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) revealed a hypoplastic right vertebral artery and an elongated and tortuous left vertebral artery as well as widened basilar artery that was compressing the brainstem (Figure 1A-C).

DISCUSSION

Based on angiography and autopsy results, the overall incidence of VBD is <0.05%, but, there is currently no data available on the exact incidence of this disorder. According to a Japanese study of people undergoing routine MRI and MRA examination, the incidence of asymptomatic VBD is 1.3% (2,3). VBD is typically asymptomatic, but approximately 6% of patients have clinical findings.

In our case of trochlear nerve paresis associated with VBD, the patient was symptomatic with head position. Furthermore, the incidence of VBD is higher in stroke patients than in normal populations, particularly in those who had posterior system infarctions (3). According to the MRI and MRA criteria described by Giang et al. (4) and Ubogu and Zaidat (5), VBD is characterized by the following: A basilar or vertebral artery diameter >4.5 mm, deviation of any portion of either arteries >10 mm from the shortest expected course, basilar and vertebral artery length >29.5 and >23.5 mm, respectively (2), or intracranial vertebral artery diameter >4 mm (4,5).

Clinical manifestations of VBD include ischemic stroke, progressive compression of cranial nerves and brainstem, cerebral hemorrhage, dizziness, ataxia, and hydrocephalus. The present case was evaluated due to intermittent trochlear nerve paresis. Symptoms can often arise after 60 years, and the development of VBD and its symptoms are correlated to atherosclerotic factors (3). Midbrain symptoms are generally due to ischemia or local compression (2). Moreover, ocular motor nerve paresis has been reported, with recurrent trochlear nerve paresis being remarkably rare (3). Herein, we present an unusual case isolated trochlear nerve paresis associated with intermittent diplopia for just 30 seconds when looking down due to a dolichoectatic basilar artery. Although there are several cases of recurrent cranial nerve paresis associated with VBD, position-related intermittent trochlear paresis has not been reported.

Intracranial arterial malformations are frequently observed. The clinical significance of these malformations is that they can cause aneurysm and VBD and are often associated with stroke. The most common arterial malformation is fenestration and is mostly found in the vertebrobasilar system. The incidence of congenital VBD is unclear, but it is estimated to be low (6).

Although the etiology of VBD is not clear, a range of potential mechanisms have been proposed. VBD can be congenital, acquired, or both. Hypertension-induced atherosclerosis may be a major factor in the development of VBD (1). Other suspected conditions include infections; congenital diseases, such as autosomal recessive polycystic kidney disease, Pompe disease, Fabry disease, sickle cell anemia, Marfan syndrome, PHACES syndrome; abnormal matrix metalloproteinase expression; male sex; smoking; and drinking (2,7-10). Our patient had no history of trauma or any disease. Pathological assessment showed rarefaction of the elastic tissue in the media with degenerated

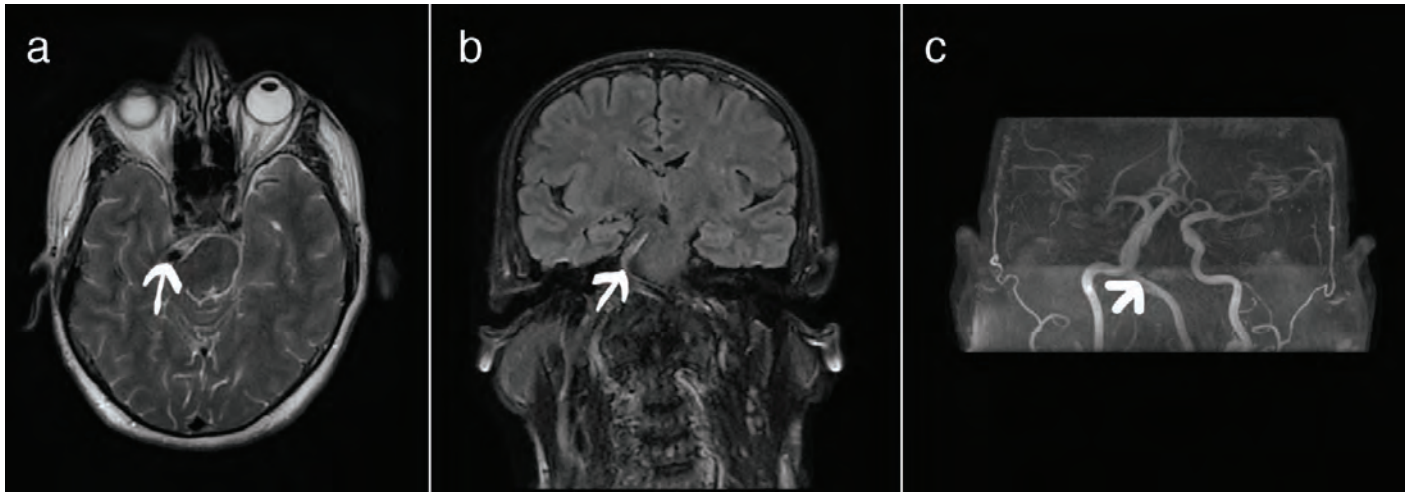

Figure 1. T1 axial magnetic resonance imaging shows a marked enlargement of the basilar artery and compression of pons (a). Widened basilar artery (b). MR angiography delineates the left vertebral artery as well as elongated and tortuous basilar artery (c)
MR: Magnetic resonance

internal elastic lamina and atrophy and reticular fiber deficiency in smooth muscle layer. Dolichoectatic arteries have an abnormally large external diameter with a thin arterial wall, sometimes containing thrombus or an atherosclerotic plaque in lumen (1,3).

VBD treatment is still controversial and is not recommended for asymptomatic patients. In symptomatic VBD cases, treatment can be decided according to the findings. In patients with hydrocephalus, shunt surgery is performed, whereas microvascular decompression and stent surgery can be performed in patients with cranial nerve findings.

Anticoagulant therapy is recommended for stroke patients or patients who are at risk of stroke (3). We did not administer any medication to our patient who showed intermittent symptoms.

Isolated trochlear nerve paresis may be associated with many factors, such as diabetes, trauma, infectious diseases, meningitis, tumors, demyelinating disease, aneurysms, stroke, and complications of cranial surgery (2,10), with trauma being the most common cause of isolated trochlear nerve paresis (2). Although there are many known causes of trochlear nerve paresis, VBD is very uncommon. Oculomotor nerve paresis is another known but rare finding. Persistent trochlear nerve paresis is even less common among patients, whereas, to our knowledge, intermittent paresis has not yet been reported (2).

Trochlear nerve paresis is associated with superior oblique muscle weakness, the clinical diagnosis of which is based on worsening vertical diplopia when reading or sitting at a table (2). Such patients must adopt a compensatory head posture. Accordingly, our patient compensated his double vision by tilting his head up.

CONCLUSION

In conclusion, isolated trochlear nerve paresis arising from VBD is a rare disorder. The findings related to the intermittent compression of the brainstem due to the basilar artery are exceptionally rare. Further, brain MRI and MRA are effective tools to identify elongation and dilatation of the vertebrobasilar system.

Ethics

Informed Consent: Was obtained as orally.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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CASE REPORT

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Dowling-degos Disease: A Case Report

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Abstract

Dowling-degos disease (DDD) is a rare genodermatose inherited as autosomal dominant trait characterized by brown to black macules located symmetrically in flexural sites. Lesions are not congenital, and the age of onset is highly variable. It is more common in women. Herein, we present the case of a male patient whose clinical and histopathological findings are consistent with DDD and then review existing literature. A 35-year-old male patient presented to the dermatology clinic with black lesions in his flexural sites since childhood. He had no subjective symptoms such as itching or pain in his symmetrically located lesions. His mother and cousins had similar lesions. On the histopathological examination of the lesion sample taken from the inguinal region, fine filiform branchings were found in the epidermis, the rete ridges showed tendency to merge, and there was budding in the rete ridges, which showed hyperpigmentation. The adjacent epidermis showed keratin cysts and mild perivascular mononuclear inflammatory cell infiltration in the superficial dermis. Based on these histopathological findings, the diagnosis was DDD. Fractional erbium YAG laser yielded good clinical outcome.

DDD should be kept in mind in the differential diagnosis of hyperpigmented lesions in flexural sites.

Keywords: Dowling-degos disease, hyperpigmentation, flexural sites

INTRODUCTION

Dowling-degos disease (DDD) is a rare pigmentation disorder and inherited as an autosomal dominant trait (1,2). The real prevalence of DDD is unknown (3). It is characterized by small round symmetrical or asymmetrical dark-brown to black pigmented macules located symmetrically, especially in flexural sites of the axillae, inguinal regions, head, neck, arms, or trunk (1,4). It may be seen in any age group, ranging from early adolescence to young adulthood. Lesions progress slowly over the years (5).

CASE PRESENTATION

A 35-year-old male patient presented to the dermatology clinic with symmetrically located black lesions on eyelids, axillae, and inguinal regions. His history revealed that the lesions were present since he was a child and did not cause subjective symptoms such as itching or pain nor regressed spontaneously. He had no complaints other than recurrent froncules in the inguinal region, and he had no history of chronic illnesses, smoking, alcohol consumption, or any medication. As regards family history, his mother and cousins had experienced similar lesions. Systemic examination and routine laboratory results were normal. Dermatological examination revealed smooth, contoured dark-brown to black macules of 2-4 mm in diameter located in eyelids, perineum, and inguinal region (Figure 1). Histopathological examination of the lesion sample taken from the inguinal region showed basket-wave orthokeratosis, fine filiform branching of the epidermis, tendency to merge in the rete ridges, and budding of the rete ridges, which showed hyperpigmentation. The adjacent epidermis showed keratin cysts and mild perivascular mononuclear inflammatory cell infiltration in the superficial dermis (Figure 2, 3).

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Despite different clinical presentation findings, reticular pigmentation disorders were taken into consideration in the differential diagnosis. Among these disorders, Galli-Galli disease was excluded because there was no suprabasal acantholysis and parakeratosis in the epidermis, Kitamura's reticular acropigmentation was rejected by the lack of atrophy in the epidermis and its specific clinical site in acral regions, and Haber syndrome was ruled out by the absence of keratotic follicles, erythema, and telangiectasias on the face. Based on his histopathological and clinical findings, he was diagnosed with DDD.

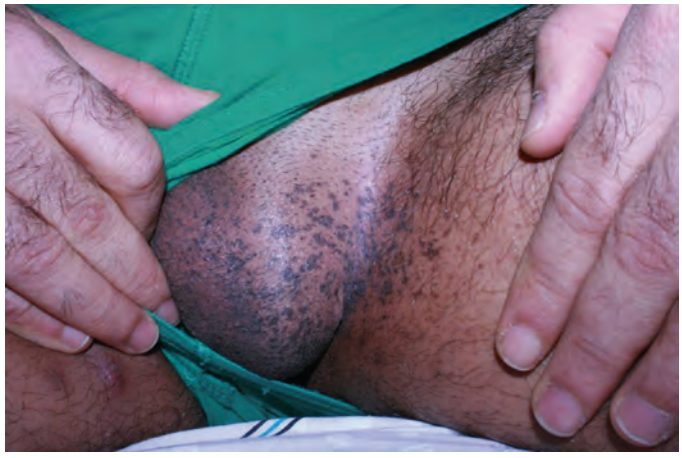

Figure 1. Dark-brown to black macules located in the inguinal region

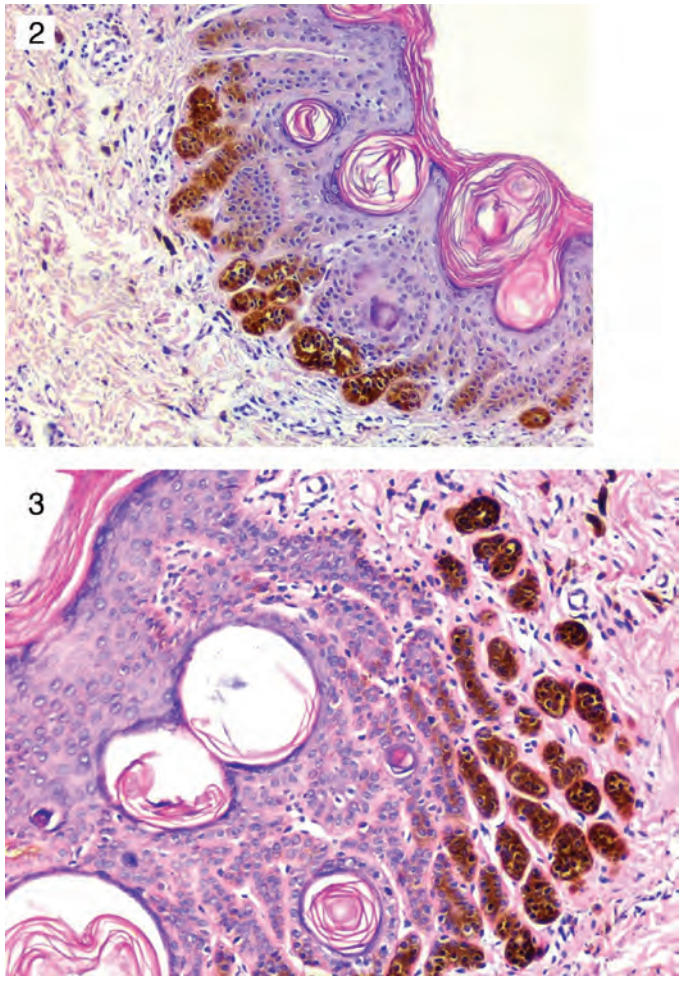

Figure 2, 3. Budding of the rete ridges, which showed hyperpigmentation. The adjacent epidermis showed keratin cysts and mild perivascular mononuclear inflammatory cell infiltration in the superficial dermis (hematoxylin and eosin staining, x200)

Two sessions of fractional erbium YAG [(Er): YAG] laser was applied to axillary lesions, which had provided good clinical outcome (Figure 4).

Informed consent was taken from the patient for the publication of this case and any accompanying images.

DISCUSSION

Recent studies have focused on the mutations of the *keratin 5* gene *(KRT 5)* in the pathogenesis of DDD (6,7). The *KRT 5* gene plays an important role in the cell-to-cell adhesion of the keratinocytes, transfer of melanosomes into the keratinocytes, transportation of organelles, and support of the nuclear structure. Because of the mutations in this gene, hyperpigmented reticular macules are seen in the body, especially in the flexural sites (6).

Although sporadic cases are reported, the patients mostly have a family history, as seen in our case (8). DDD is thought to be inherited as an autosomal dominant trait, but in published series and cases, it is more commonly seen in women than in men. As a rare disorder, only a few cases are reported in our country, and the number of the affected women appeared higher than that of men (4,9). In our case, the patient is also a male.

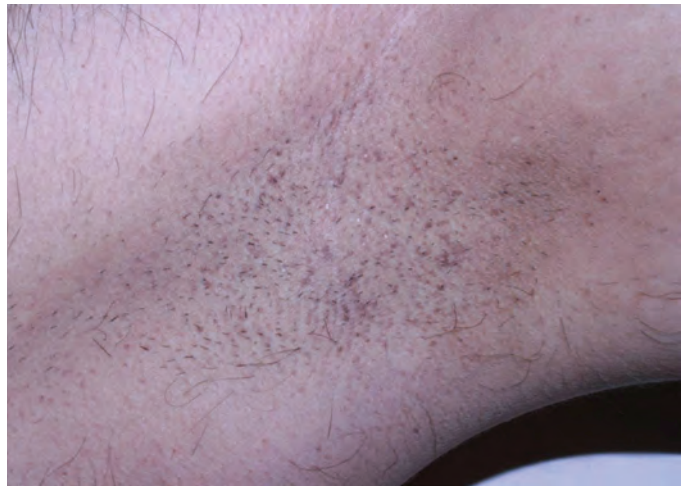

Figure 4. Axillary region after treatment

The age of disease onset is variable. It may be seen in any age group, ranging from early adolescence to young adulthood. Most of the cases are seen within the fourth decade (1). In our case, the lesions were present since childhood.

In DDD, lesions arise from the flexural sites and slowly spread to other sites. The axillae, inguinal regions, face, neck, arms, and trunk are mostly commonly affected. Other clinical findings that are less commonly seen in patients with DDD are atrophic scars around the mouth, comedone-like lesions in the face, neck and trunk, and epidermal and trichilemmal cysts (1,2). None of these findings were observed in our patient.

Histopathological findings specific to DDD are elongation of the rete ridges, filiform formation, interconnecting branching, and basal hyperpigmentation. Follicular infundibulum may be involved. Moderate orthokeratosis or hyperkeratosis, melanophages in the papillary dermis, and mild perivascular mononuclear inflammatory cell infiltration may be seen (1). Most of the defined findings were also seen in our case.

Other reticular pigmentation disorders such as Galli-Galli disease, Kitamura's reticular acropigmentation, and Haber syndrome were taken into consideration in the differential diagnosis (5,10). In Galli-Galli disease, which is a variant of DDD, besides the characteristic histological findings, suprabasal dyskeratotic acantholysis is also present. In Kitamura's reticular acropigmentation, atrophic hyperpigmentated papules begin on the outer surfaces of acral areas such as in hands and feet. In Haber syndrome, the first lesions are facial eruptions. Some studies have shown that all these diseases are inherited as autosomal dominant trait and may show similar clinical and histopathological findings and a patient may present with more than one of these diseases; therefore, these diseases should be evaluated within the same spectrum (11). The differential diagnosis also includes neurofibromatosis type 1 and acanthosis nigricans (3). Although the lesions in the axillary and inguinal areas in neurofibromatosis type 1 may show similarity to DDD, the presence of multiple neurofibromas is one of the important findings in the distinction. In acanthosis nigricans, there is no reticular pigmentation, as seen in DDD.

Till date, DDD has no known definitive treatment. Some studies have reported that topical steroids, azalaic acid, topical retinoids, depigmentation agents, and laser therapies especially CO_2 or Er: YAG laser are effective treatment of DDD (8,12,13). In the present case, two sessions of fractional Er: YAG laser was applied to the axillary as treatment and had provided good clinical outcome.

CONCLUSION

Since DDD is a rare disease that predominantly affects women and reported cases are limited, this condition should be kept in mind in the differential diagnosis of hyperpigmented lesions of flexural sites, not only in women but also in men. As there is no known definitive treatment, development of new treatment modalities is warranted.

Ethics

Informed Consent: Informed consent was taken from the patient for the publication of this case and any accompanying images.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ş.E., T.Y., P.E.Z., Concept: S.Ş.E., T.Y., P.E.Z., Design: S.Ş.E., T.Y., P.E.Z., Data Collection or Processing: S.Ş.E., T.Y., P.E.Z., Analysis or Interpretation: S.Ş.E., T.Y., P.E.Z., Literature Search: S.Ş.E., T.Y., P.E.Z., Writing: S.Ş.E., T.Y., P.E.Z.

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

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