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CONTENTS

EDITORIAL

Dear readers,

On the behalf of our team, I am very proud of publishing the very first issue of the year 2021. In this issue, you will find 11 articles: consisting of 1 editorial, 2 reviews, 4 original articles, and 4 case reports. Below you can find quick synopses for these articles.

In the reviews, Malik et al. describes the symptoms, diagnostic criteria, impact on daily life and management of body dysmorphic disorder. Manan et al. expands on the implications of artificial intelligence in the field of radiology.

In our original articles, Tan et al. aims to determine the level of COVID-19 fear among Turkish medical students in order to assess the mental health statuses of university students during the pandemic. Meanwhile, in the interest of treating diabetic retinopathy, the most common preventable cause of blindness in the working-age population, İzzettinoğlu et al. shares their findings on treatment regimens for the prognosis and progression of diabetic retinopathy and visual acuity. Kaygısız et al. investigates the evaluation of toilet habits and self-awareness of constipation statuses among young adults; and Akay et al. presents a dataset including demographic features, disease characteristics, and survival rate of follicular lymphoma patients.

Of our 4 case reports, Cengiz et al. presents a case of an incidental unicentric Castleman disease. By presenting this case of unicentric Castleman disease they aim to raise awareness for a rare disease. İşkan et al. presents a case report of an incidental finding of breast cancer using Tc-99m MIBI scintigraphy. Yılmaz et al. shares a rare syringomyelia case which necessitated a revision surgery due to the migration of the T-tube into the syrinx cavity. Finally, Tan et al. presents a treatment approach to a rare case of squamous cell carcinoma of the nasal septum.

As the new year begins, new editors have joined our editorial team: Defne Erçelen from the University of California, Los Angeles, Berna Arda from Ankara University, and Necdet Süt, Elif Çalışkan, Eylül Şenödeyici, Janset Özdemir, Pınar Tuncer, and Ceren Yüksel from Trakya University. I believe that they will be great additions to our team and work to increase the quality of our journal.

Lastly, I would like to thank all of the editorial board who contributed to this issue.

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BODY DYSMORPHIC DISORDER: A COMPREHENSIVE REVIEW

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ABSTRACT

Body dysmorphic disorder is psychiatric morbidity that comes under the spectrum of obsessive-compulsive disorders. Individuals suffering from body dysmorphic disorder are incredibly concerned about their minor or so-called defects to such an extent that their lives may be affected drastically. As a result of continuously thinking about the asserted defect, the individuals end up suffering from major depression, anxiety, and self-harm. Diagnosis of body dysmorphic disorder is based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria. The management of body dysmorphic disorder consists of psychotherapeutic and pharmacological interventions. Body dysmorphic disorder is a hidden disorder and is often under-reported. It has been linked to muscle dysmorphia, substance abuse, and major depressive disorder. The lack of studies in different countries and populations has made this a topic that requires substantial input from researchers. ***Keywords:*** Body dysmorphic disorder, obsessive-compulsive disorder, somatoform disorders

INTRODUCTION

Negative statements regarding appearance often posses the potential of having an detrimental impact on one's self-confidence. However, when these comments are self-made and focused on a non-existent defect, they constitute a disorder called body dysmorphic disorder (BDD) (1). BDD first appeared in the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders, third edition, under the name 'dysmorphophobia' in 1987 (1). Diagnostic and Statistical Manual of Mental Disorders, fourth edition, and International Classification of Diseases-10 (ICD-10) placed BDD under "somatoform disorders", while today, BDD is depicted in Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), under the obsessive-compulsive spectrum (2, 3).

According to APA, BDD is a mental disorder characterized by an individual's preoccupation with a slight or non-existent defect to such an extent that it causes significant distress and impairs their functionality (4).

The presence of BDD varies globally from 1% to 2% in different cohorts, and the incidence rate is higher among females (5). The foci of concern vary among the affected individuals. Distressing appearance traits can include weight, head hair, skin, nose, teeth, and height (6, 7). The patients suffering from body dysmorphophobia undergo a daily struggle to achieve the perfect body type. The increasing popularity of taking selfies, coupled with a lack of self-confidence, often drives them to undergo cosmetic modifications in order to achieve a flawless look. This was termed as "Snapchat dysmorphia" (8). Individuals with BDD demonstrate an excessive preoccupation with their defect to a degree where this affects their mental health. This leads them to be depressed and can often contribute to the development of suicidal predilections. Due to a similarity of presentation, BDD can be misdiagnosed as major depressive disorder (MDD) or obsessive-compulsive disorder (OCD) leading to wrong treatment strategies (9). This review aims to provide an overall picture of BDD, its symptoms, diagnostic criteria, its effect on daily life, and management.

SYMPTOMS OF BODY DYSMORPHIC DISORDER

There are four main symptoms of BDD, which manifest in different ways (4). The symptoms are as following: preoccupation with the perceived or concerned; repetitive behaviors such as checking their appearance on a reflective surface, application of various products to hide the defect, skin picking, obsessive dietary habits, and thoughts of getting cosmetic surgery to rectify the defect; delusional beliefs such that people are mocking their appearance based on the defect. Consequential symptoms such as low self-confidence, avoidance of public places due to a fear of being judged, anxiety, and depressive symptoms where suicidal thoughts may be seen as well (4).

DIAGNOSTIC CRITERIA

Body dysmorphic disorder remains an under-diagnosed and inadequately treated disorder, despite being a common mental illness (10, 11). The timely diagnosis of BDD is crucial for the proper management of the disorder. The ICD-10 lists BDD under the category of somatoform disorders (2). The diagnosis of BDD is commonly based on the DSM-5 criteria. It is being used in classifying as well as a diagnostic tool. It is published by the APA and serves as the principal authority for the diagnosis of psychiatric disorders.

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The DSM-5 criteria classify BDD in the chapter of "Obsessive-Compulsive and Related Disorders," along with OCD and several other disorders (12). The DSM-5 diagnostic criterion for BDD is summarized in Table 1 (13).

Body Dysmorphic Disorder Questionnaire and Body Image Disturbance Questionnaires are used for identifying BDD. They consist of a series of questions that assess an individual's perception and concerns about their physical appearance and the negative impact of those concerns on a person's life (14-16). BDD is diagnosed by mental health professionals/psychiatrists through structured interviews based on Structured Clinical Interview for DSM-5, BDD Diagnostic Module, or Body Dysmorphic Disorder Examination (BDDE). The severity of BDD can be assessed using scales such as the Yale-Brown Obsessive-Compulsive Scale Modified for Body Dysmorphic Disorder, the Psychiatric Status Rating Scale for Body Dysmorphic Disorder or BDDE. Scales called the Brown Assessment of Beliefs Scale and Overvalued Ideas Scale can be used by psychiatrists to gain further insight into BDD (14-16).

Body dysmorphic disorder can be misdiagnosed as OCD, social anxiety disorder, trichotillomania (hair-pulling disorder), MDD, excoriation (skin-picking disorder), eating disorder, or generalized anxiety disorder (16). Such misdiagnosis can hamper adequate treatment.

GLOBAL PICTURE OF BODY DYSMORPHIC DISORDER

Table 2 aims to provide a picture of some studies around the globe with varying populations. Researches are carried out globally trying to find out prevalence of BDD in different groups. A systematic review published in 2016 provided a comprehensive analysis of BDD among various study populations (17). It was found that the weighted prevalence of BDD in the adult population was 1.9%, followed closely by adolescents with 2.2%, where the student population reported a higher prevalence with 3.3% (17). The weighted prevalence was found most elevated among the population undergoing rhinoplasty (20.1%) and general cosmetic surgery (13.2%) (17).

EFFECTS OF BODY DYSMORPHIC DISORDER ON LIFE

Living with BDD means living with a distorted image of one's own body, low self-esteem, and thus having difficulty in accepting the way they look. The detrimental impacts of BDD stated down below make it evident that early diagnosis and treatment of this disorder are necessary to prevent future complications and consequences. Further long-term prospective studies are needed to study these side effects more profoundly. Figure 1 provides an overview of the detrimental effects of BDD.

Body dysmorphic disorder influences students' life

Body dysmorphic disorder might affect multiple aspects of an individual's life, including sleep, appetite, academics, occupation, and/or social life. The negative impact of BDD on academic life of students is evident by the fact that around 22.2% of adolescents suffering from BDD reported dropping out of school, either temporarily or permanently (29). This could be attributed to the exhaustion caused by excessive preoccupation with their non-existent defect, leading them to have a reduced and poor quality of sleep. Thus BDD has negative consequences on the overall health and quality of students lives (30, 31).

Table 1: Diagnostic criteria of body dysmorphic disorder according to DSM-5 (13).

Diagnostic Criteria of BDD According to DSM-5	
Appearance preoccupations	The individual must be preoccupied with a defect or flaw in his/her physical appearance that either does not exist or, if present, is not a matter of concern to others, and the affected individual at least spends an hour a day thinking about the perceived defect.
Repetitive behaviors	There should be a history of the individual performing repetitive, compulsive behaviors about the concerned defect, such as excessively checking out oneself in the mirror, asking others about the perceived defect, pinching or touching the concerned flaw, or comparing oneself with others.
Clinical significance	The perceived flaw must have unhealthy severe ramifications on the health of the individual and cause severe distress on the personal, social, and occupational life of the individual.
Differentiation from an eating disorder	If the preoccupations are related to the bodyweight of the individual such that the main focus of concern is being too fat or too thin, any other eating disorder should be ruled out. If the criteria of any eating disorders are met, the correct diagnosis should be made.
Specifiers	Once the diagnosis of BDD has been made, the following two specifiers should be considered to identify the subgroups of BDD: ***1) Muscle dysmorphia:*** This variant of BDD is diagnosed if the individual displays concerns of being too lean or not muscular enough and develops an obsession with bodybuilding and weightlifting to improve his build. Such individuals have been reported to be more suicidal and prone to substance abuse than those with other forms of BDD. ***2) Individual specifier:*** This specifier stipulates the degree of insight an individual has and is classified into three categories: • *With fair insight:* The individual acknowledges that the body dysmorphic beliefs are not true or may or may not be true. • *With poor insight:* The individual considers the dysmorphic beliefs to be true. • *No insight present/ delusions:* The individual has a firm conviction about the presence of the dysmorphic belief.

BDD: *Body Dysmorphic Disorder*

Table 2: A review of some studies from different countries on body dysmorphic disorder (18-28).

Study	Location	Study population	Number of participants			Mean age (years)	Screening tool	BDD prevalence			Comments
			Total	Male	Female			Total (%)	Male (%)	Female (%)	
Cansever A et al. (18)	Turkey	Female nursing students	420	0	420	19.1	DSM IV BDDE	4.8	0	4.8	Diagnosis of BDD was made on an interview using BDDE.
Koran ML et al (19)	USA	Adult population	2048	739	1309	Most participants were ≥55 years*	DSM IV BDD phone interview	2.4	0.8	1.6	Men were most worried about 'hair' and women about 'stomach.'
Liao Y et al. (20)	China	First year medical students	487	181	306	18.5	DSM IV criteria BDDQ, DCQ	6	0	6	Other additional scales used in the study are BSQ, SMAQ, SIAS, and SDS.
Conrado LA et al. (21)	Brazil	Dermatologic patients (300) and controls (50)	350	71	279	42.2	BDDQ-DV	9.1	N/A	N/A	BDD was more common among individuals seeking dermatologic treatment (n=31) as compared to the control group (n=1).
Barahmand U et al. (22)	Iran	Students from final year of high school to first two years of university	843	463	380	18.1	MBSRQ-AS	19.1	6.6	12.5	12.9% of the population had comorbid social anxiety, while 6.4% had comorbid obsessive beliefs. Females reported more social anxiety, while males reported more obsessive beliefs.
Fathololoom MR et al. (23)	Iran	Rhinoplasty patients	130	31	99	26.4	BDDQ	31.5	N/A	N/A	Among BDD patients, 29.3% had coexisting depression, and 26.8% had coexisting anxiety.
Brohede S et al. (24)	Sweden	Adult females	2885	0	2885	Age:18-30 (29.2%); 3-45 (36.4%);46-60 (34.4%)*	DSM IV BDDQ	2.1	0	2.1	Depression and anxiety were measured using HADS. The age group of 18-30 years had higher BDD prevalence.
Schneider SC et al. (25)	Australia	Adolescents	3149	2000	1149	14.6	DSM IV BDDQ-A	1.7	N/A	N/A	The three most commonly disliked body parts are skin, nose, and hair, respectively.
Ahamed SS et al. (26)	Saudi Arabia	Female medical students	365	0	365	20.0	BIDQ	4.4	0	4.4	SIAS scale was used. No significant association between BDD and social anxiety was found. Participants were most concerned about their skin.
Buhlmann U et al. (27)	Germany	General population (18-93 years)	2510	1142	1368	46.9	DSM IV BDD	1.8	7	1.1	BDD affected individuals had a higher frequency of suicide ideation and suicide attempts compared to non-BDD individuals. History of cosmetic surgery was more often reported by body dysmorphic individuals
Jangda AA et al. (28)	Pakistan	University students	280	0	280	22.5	DSM-5 BIDQ	8.1	0	8.1	BDD was prevalent among female university students, and weight was the major focus of concern.

N/A: *Not Available,* ***BDD:*** *Body Dysmorphic Disorder,* ***BDDE:*** *Body Dysmorphic Disorder Examination,* ***BDDQ:*** *Body Dysmorphic Disorder Questionnaire,* ***BDDQ-A:*** *Body Dysmorphic Disorder Questionnaire– Adolescent Version,* ***BDDQ-DV:*** *Body Dysmorphic Disorder Questionnaire Dermatology Version* ***BIDQ:*** *Body Image Disturbance Questionnaire,* ***BSQ:*** *Body Shape Questionnaire,* ***DCQ:*** *Dysmorphic Concern Questionnaire,* ***DSM-IV:*** *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition,* ***DSM-5:*** *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* ***HADS:*** *Hospital Anxiety and Depression Scale,* ***MBSRQ-AS:*** *Multidimensional Body–Self Relations Questionnaire Appearance Scales,* ***SDS:*** *Self-Rating Depression Scale,* ***SIAS:*** *Social Interaction Anxiety Scale,* ***SMAQ:*** *Swansea Muscularity Attitudes Questionnaire*
*Mean age was not available and study data has been reported.

Body dysmorphic disorder and weight concerns

Young individuals believe that they are over or underweight, which leads to body dysmorphia and excessive dietary habits or participation in exhaustive exercises (32). Muscle dysmorphia is a variant of BDD, which is characterized by the development of obsessive thoughts related to one's build. The affected individual aims to exercise and develop more muscle and may even use anabolic steroids. This obsessive habit of bodybuilding may lead to functional impairment later in life (33).

Adolescents who have higher body-mass index are excessively concerned about their body image and have low self-esteem as well as identity issues. Years of struggling with obesity, stigmatization, and peer pressure may lead to an increased negative perception, and eventually having bariatric surgery (34).

Substance abuse in individuals with body dysmorphic disorder

History of different forms of abuse has been reported by individuals of various ages suffering from BDD. A study by Didie et al. (35) showed that a large number of BDD patients (78.8%) went through some form of child neglect, emotional neglect, or abuse either emotional, physical, or sexual. Thus a link between the development of BDD and history of abuse was noted. Individuals with a history of abuse and BDD are likely to suffer from mood disor-

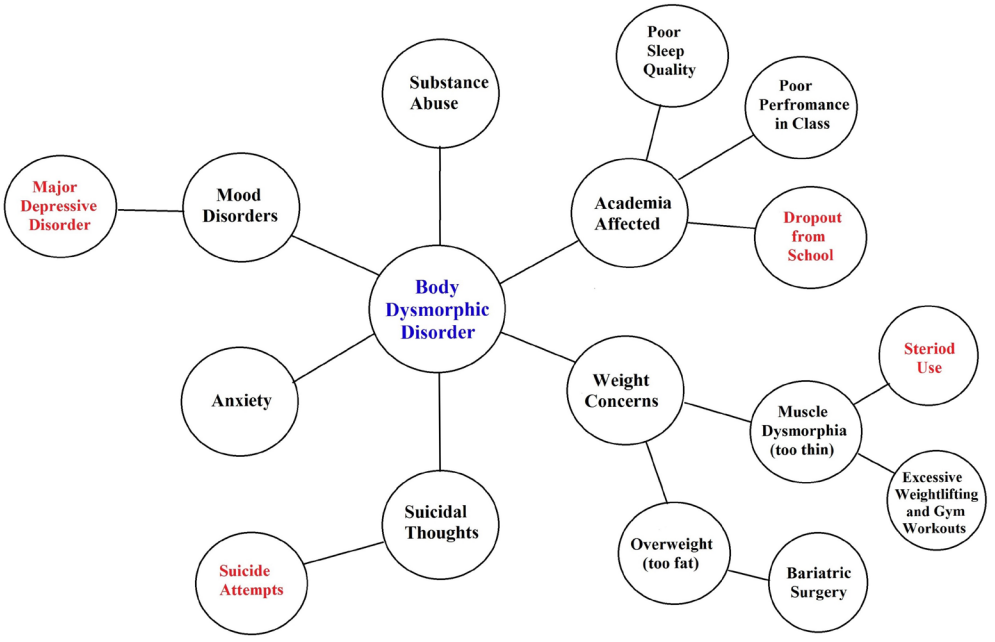

Figure 1: Impacts of body dysmorphic disorder on different aspects of life.

ders, substance abuse, and suicidal thoughts in their adult life (35). Grant et al. (36) reported that 48.9% of BDD patients had a lifelong history of substance use disorder and 35.8% developed a lifetime substance dependence, mostly alcohol dependence (29%). Another crucial fact was that 68% of the people have remarked that BDD had contributed to their habit of substance abuse. It was also seen that individuals with BDD and a coexisting substance use disorder showed a higher rate of suicide attempts compared to those with just BDD (38.4% vs. 18.9%) (36).

Major depressive disorder and body dysmorphic disorder

Body dysmorphic disorder and OCD have been grouped as Obsessive-Compulsive Related Disorders in the DSM-5. A study investigating the relation of these disorders to anxiety and shame showed that anxiety is an important risk factor for the development of both of these disorders (37). MDD is common in people with BDD, and thus a progressively worsening BDD may hint at a presence of coexisting MDD (38). Individuals with BDD demonstrate an excessive preoccupation with their perceived defect to a degree that affects their mental health. This leads them to be depressed and can often contribute to the development of suicidal predilections (37, 39, 40). A disturbing aspect of this disorder was demonstrated in a review by Phillips et al. (41) showing that 80% of the affected individuals had suicidal thoughts, and 24-28% even attempted suicide.

MANAGEMENT OF BODY DYSMORPHIC DISORDER

The need for a recognition and management of BDD is urged upon due to several reasons. According to a research by Beilharz et al. (42), the suicidal tendency of a person suffering from this disorder was found to be about 45 times more than the average individual. BDD has been also linked with mood swings, anxiety, depression, and various mental disorders (42). Research conducted by Grant et al. (36) associated BDD with substance abuse, where almost half of the patients developed a lifetime habit of drug abuse. These alarming consequences of an untreated BDD stress the importance of its timely diagnosis and proper treatment.

Treatment options for BDD include both psychotherapeutic and pharmacological interventions. Recent studies have deemed cognitive-behavioral therapy (CBT), selective serotonin reuptake inhibitors (SSRIs), or a combination of the two as the treatment for BDD (12). CBT is a type of psychosocial talk therapy that identifies maladaptive thoughts and emotional responses and substitutes them with desirable patterns of thinking and behavior. The objective of CBT is first to recognize the problem, then challenge and reverse the harmful thoughts or habits and finally result in an improved quality of life. The goal is also to familiarize the patient with coping mechanisms and prevent future relapses. A standard CBT consists of 12-22 weekly sessions and 3 to 6 months of follow-up sessions. Ample data is available, concluding CBT is the most successful and accepted management option when treating BDD (43, 44).

Selective serotonin reuptake inhibitors, typically used as antidepressants, are used in the treatment of several psychiatric disorders such as depressive and anxiety disorders, social phobias, eating disorders, and panic disorders as well. More commonly used drugs of the class are fluoxetine, paroxetine, escitalopram, among others. These drugs work by limiting the reabsorption of serotonin, thus increasing its extracellular levels. Numerous studies have highlighted the importance and success of SSRIs in the improvement of symptoms and the treatment of BDD (43, 45).

However, along with the efficacy of the treatment, it is crucial to keep an eye on the adverse effects of long-term antidepressant therapy. More common side effects include nausea, vomiting, insomnia, agitation, weight gain, and sexual problems. In contrast, several serious adverse effects can also occur. These adverse effects can be listed as hostility towards others, suicidal tendencies, psychosis, and seizures (43). These side effects often cause significant challenges with treatment adherence. Since BDD is a chronic disorder and demands long-term therapy, continuous monitoring is crucial to avoid the earlier-mentioned side effects of SSRIs. The management of BDD is summarized in Figure 2.

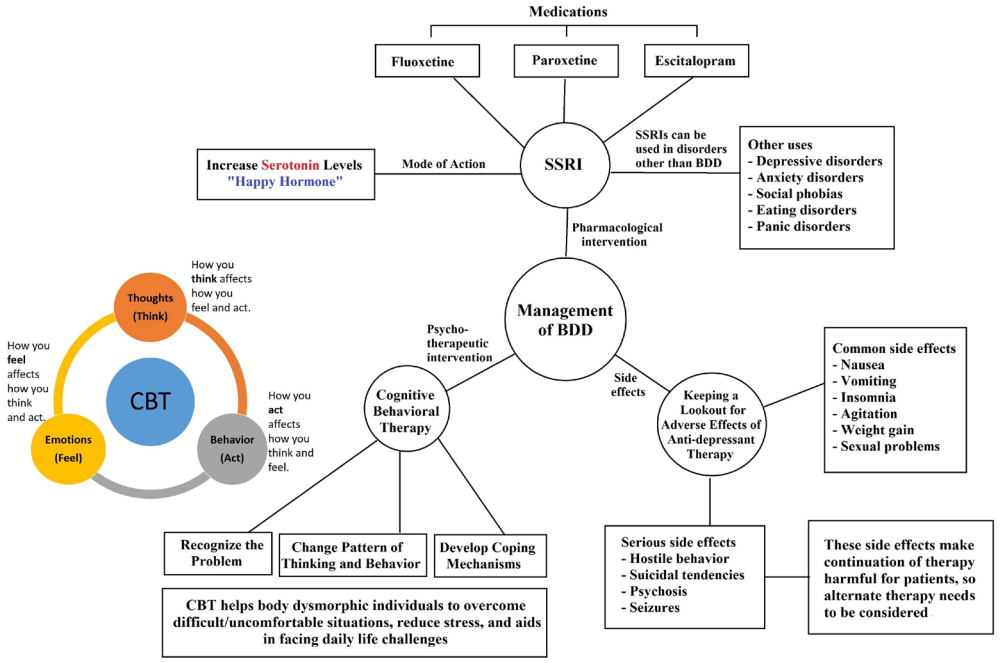

Figure 2: Management of body dysmorphic disorder.
BDD: *Body Dysmorphic Disorder,* ***CBT:*** *Cognitive Behavioral Therapy,* ***SSRI:*** *Selective Serotonin Reuptake Inhibitors*

FUTURE PROSPECTS AND SUGGESTIONS

The fact that BDD is not only prevalent but also a seriously damaging condition makes it essential to develop a thorough understanding of the disease. Since most people share just the best parts of their life via social media, it is tough to avoid making comparisons.

On our path to understanding BDD, our first step should be destigmatizing and creating awareness among the general population as well as the health care professionals. Countrywide awareness campaigns and more research should be held on this disorder. Encouraging body positivity and conducting sessions with various psychotherapists may be beneficial for the patients. Avoiding misdiagnosis could accelerate the treatment progress. Many patients are often misdiagnosed with MDD or OCD and that results in wrong treatment strategies (9). After the prompt diagnosis, the treatment should be planned according to the patients' needs; pharmacological treatment and/or cognitive behavioral therapy. Encouraging students with symptoms of BDD to schedule appointments with mental health professionals may avoid serious consequences as well.

The development of self-confidence concerned with one's appearance is a great contributor to an individual's personal and professional growth. Thus, the development of a negative self-image not only harms a person in his/her current life but also hinders his/her future growth. Still, further studies are needed to prove if this disease becomes an obstacle in the path of academic success.

CONCLUSION

In conclusion, BDD is a complicated disorder that harms an individual's life in many ways. It can lead to very low self-esteem, extreme anxiety, depression, and suicidal ideation in an individual. It can affect students emotionally as well as academically and can even lead to dropouts from school. It is crucial to identify this disorder and educate people about body-positivity. Correct diagnosis and adequate management can help the affected individual to have a healthy life again.

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A MODERN RENAISSANCE OR AN ETHICAL CONUNDRUM: REVIEWING THE IMPLICATIONS OF ARTIFICIAL INTELLIGENCE IN THE FIELD OF RADIOLOGY

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ABSTRACT

Recent progress in the field of artificial intelligence has found its way into the diverse realms of medical imaging and radiology, raising questions regarding its potential, efficiency, accuracy, and reliability. This review aims to educate radiologists and medical students regarding the uncharted world of artificial intelligence through the discussion of its achievements in radiology while keeping an ethical and prognostic outlook in mind. Artificial intelligence, through the application of its subsets (i.e. machine learning and deep learning), has caused vast expansions in radiology, such as automating diagnoses. Pneumonia, pneumothorax, pulmonary tuberculosis, pulmonary nodules, etc. can now be detected through the use of various artificial intelligence algorithms. However, the acceptability of these highly accurate systems is still a matter of massive doubt. Educating the healthcare professionals in this regard would alleviate the fear of an unknown computing system while also answering numerous misconceptions. Moreover, with acceptability comes a huge moral and ethical responsibility. Ethical codes need to be devised that provide appropriate solutions to the moral problems connected with artificial intelligence. Thus, with all of these factors under consideration, artificial intelligence has enormous potential in the field of radiology and will broaden the horizon of healthcare professionals by creating a greater number of computing-related opportunities. ***Keywords:*** Artificial intelligence, radiology, ethics, deep learning, machine learning

INTRODUCTION

The past century has inarguably added numerous technological advancements to the list of developments in the field of radiology and medical imaging. The recent progress made in the young yet thriving field of artificial intelligence (AI) has shown that it has not only earned its place on this list but has created opportunities for future developments as well. With the use of machine intelligence, AI technology is capable of receiving, processing, and interpreting external data. However, the ability of AI to learn from said data and use it towards the achievement of certain goals while being able to flexibly remodel, readjust, and transform, is what makes it unique. Hence, AI mainly deals with the advancement of computers that can partake in intellectual processes similar to those of a human being (1).

Radiologists are particularly interested in the aspects of AI concerned with high-level visual processing through the use of computers. The field that can materialize this interest is conveniently termed as 'Computer Vision' (2). The deep model of most interest in this regard is object detection through the use of a 'Convolutional neural network' (CNN); which imitates the ability of a human brain to process information by developing a multilayered organized network of neurons (3). Deep learning is a subclass of machine learning and is persuaded by the process of image recognition and interpretation in the human brain (4, 5). Classical machine learning requires human intervention between its two phases (extraction of features and classification of image), but deep learning uses a multilayered artificial architecture of neurons to realize its set goals and does not require any human intervention (5). Machine learning is essentially the basis for computer-aided diagnosis (CADx); which was developed to assist image reading (3). Both of these novel fields fall under the broad classification of AI technologies and find immense potential in medicine as well as surgery. As seen, changes are inevitable in the ever-growing field of radiology with the advent of higher degrees of machine intelligence. Therefore, a strong sense of innovation and adaptability must be ingrained in the minds of radiologists in order to assist their traditional diagnostic practices with the technological advancements in their field.

WHERE DO WE STAND CURRENTLY?

The importance of diagnosis made on radiological data (X-ray, computerized tomography (CT), ultrasonography, magnetic resonance imaging (MRI), etc.) is undeniable in the management of clinical patients, but according to the World Health Organization, two-thirds of the world population lacks access to radiological diagnostics (6). There is also a shortage of experts who can interpret radiographs even if the availability of imaging equipment is made certain (3). The incorporation of AI has a vast scope in areas suffering the impacts of such shortages.

Among the medical imaging techniques performed annually, the chest radiograph is the most common modality with 2 billion procedures performed each year (7). Hence, there is a large number of datasets of chest radiographs that is available to researchers

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working on the development of AI systems. Using this modality, the currently available models can detect clinical anomalies, such as pneumonia, mass, edema, and fibrosis, with performance potential comparable to a practicing radiologist (8). Scanning of chest radiographs and flagging of suspicious ones containing moderate to large pneumothorax has also been made possible by a deep CNN algorithm. This algorithm was successfully able to detect 80-84% of the images showing moderate to large pneumothorax but failed to detect smaller anomalies since the algorithm had not been trained to do so (9). Artificial intelligence also becomes prominent in the refinement of workplace dynamics by tagging radiographs with potential abnormalities, resulting in prompt identification of anomalies by the radiologist and prioritization of the patients based on the urgency of treatment and severity of their disease. The reporting turnaround time for chest examination was reduced by 44% with the development of a Computer-aided detection (CADe) system that automatically detects abnormal chest radiographs by using density and textural features (10). Following this point, extensive researches conducted in the development of AI technologies to diagnose various radiologically detectable thoracic anomalies have been reviewed to provide a detailed outlook on the potentials of this growing field.

Lung Cancer

Lung cancer is the most prevalent form of cancer and is also responsible for 18% of the deaths caused by all cancers; thus, adding to the fact that it is cancer that causes the most deaths globally (11). The development of DeepConvSurv has aided the utilization of Convolutional neural networks (CNNs) in the survival prediction of patients suffering from lung cancer (12). This prediction was made possible based on pathological images. Moreover, extensive experimentation has also established the superiority of using CNNs for survival prediction (12). An accuracy of 82.5% in detecting lung cancer was obtained by Paul et al. (13), using a pre-trained CNN and merging it with a quantitative approach by extracting features from CT images. The deep learning-based algorithm developed by Nam et al. (14), was able to outperform the physicians in the detection of malignant pulmonary nodules and, when used as a second reader resulted in enhanced nodule detection ability in all physicians.

Pulmonary Nodule

For timely detection and management of lung cancer, the identification of pulmonary nodules is a crucial factor. Pulmonary nodules are the early manifestations of lung cancer and are often classified on chest radiographs as small circular low contrast masses of tissue characterized by a wide variety in size and density (15). A major application of the CADx system is the diagnosis of pulmonary nodules on the radiograph. The computer-aided diagnosis systems are classified into two major groups; CADe and CADx (16). Oftentimes a combination of both CAD systems is used. A CADe scheme, with a sensitivity of 76% on a dataset of the Japanese Society of Radiological Technology (JSRT) and 77% on a University of Chicago dataset was developed to detect nodules on chest X-ray (CXR), and it can potentially improve the nodule detecting abilities of the radiologists as well (15). Additionally, the author acknowledged that the higher sensitivity was obtained with the dataset of the University of Chicago since the average nodule size was larger and quality of the digitally obtained images was better when compared with the JSRT dataset (15). To establish that the CAD system (the combination of CADe and CADx) is clinically useful to the radiologists in detecting pulmonary nodules, an observer performance study was conducted by Kobayashi et al. (17), which resulted in the successful trial of 16 radiologists and resultantly, showed statistically significant improvement in the radiologists' performance to detect lung nodules when the CAD scheme was utilized.

Pneumonia and Pulmonary Edema

Lung areas appear white or light gray on CXR when the patient is suffering from pneumonia. The sputum or water-filled lung areas absorb more radiation resulting in the color change. Using this approach, the physicians can ascertain the degree of infection. A deep learning algorithm called 'Chexnet' was trained by Rajpurkar et al. (18) and its comparison was made with the performance of practicing radiologists. The result indicated outperformance of the algorithm in comparison to an average radiologist (18). The use of CNN in the detection and location of pulmonary edema has also been made possible (19).

Tuberculosis

Tuberculosis (TB) is one of the top 10 leading causes of death resulting in 1.4 million deaths worldwide and 10 million patients being infected in 2019 (20). The abnormal manifestation of TB on CXR results from the variations in the lung texture and geometry, such as consolidations, infiltrations, and cavitation. Different types of manifestations make it difficult to detect TB on CXR, thus, algorithms that focus on different manifestations need to be combined. The prevalence of TB in low-to-middle income areas is relatively high, making the automation of its radiological diagnosis necessary in those zones; since expert radiologists are often lacking there as well (21).

A multitude of different appearing TB manifestations has to be detected in order to achieve an accordant result in different populations. Textural, focal, and configurational abnormality analyses have been used in combination to achieve automatic detection of TB on a CXR (22). Furthermore, the development of a deep learning-based automatic detection algorithm has not only aided the diagnoses of active infections of pulmonary TB but has also outperformed physicians, including thoracic radiologists (23).

Retraining of two deep convolutional neural networks (DCNNs), AlexNet and GoogLeNet, have accurately classified TB on chest radiograph. The best performing classifier, obtained by combining both DCNNs, had an area under the curve of 0.99 (24). But as addressed by the author, the model was initially trained to differentiate between normal and abnormal CXR with regards to TB and may give a false-positive result in pathological conditions with presentations similar to TB on imaging (24). This limitation confines the use of these algorithms in areas where TB is endemic, such as underdeveloped areas.

Chronic Obstructive Pulmonary Disease

Computerized tomography (CT) is the medical imaging technique that is ideal for the characterization and diagnosis of emphysema and airway diseases (25). One of the earlier techniques involved in the detection of emphysema called density mask analysis was unable to differentiate between the subtypes of emphysema (26). Visual inspection can overcome this limitation but in doing so implicates its shortcoming: interobserver variability can not be ruled out during visual inspection (27).

To overcome these challenges, the trend has shifted towards textural analysis using machine learning. Various features are extracted from the region of interest on the lung field and then subjected to categorization. This technique was used successfully in the classification of various obstructive patterns of the lung parenchy-

ma, but recently, deep learning has taken over and proven to be more advantageous; since using the deep learning algorithms has allowed for the task to be completed without any human interposition (28). CNNs have been used in the classification of emphysema using textural analysis with higher classification rates (29).

The use of CNNs in the diagnosis of chronic obstructive pulmonary disease has proved to be of value but building a CNN from scratch requires large computing resources and extensive availability of datasets, which is difficult to obtain in medical science (28). However, it has been shown that the use of a pre-trained CNN with fine-tuning detected pulmonary embolism more accurately than a CNN developed from scratch (30). Thus, the use of transfer learning, as well as fine-tuning pre-trained CNNs could prove to be more efficient and effective in detecting various other conditions.

A LOOK INTO THE ETHICAL OBSTACLES

The ultimate goal of a healthcare practitioner is to ensure an efficient delivery of the best possible outcome for the patient, and so both the radiologist and the autonomous AI system need to follow a set of rules that directs positive results in favor of the patients. Additionally, three prime ethical points of concern have been identified while recognizing the moral implications of AI technology; safety, judicial transparency, and privacy (31). While dealing with technology, these are crucial points of a potential contravention when neglected.

The essence of medical ethics is formed around the fulfillment of patient safety through the accurate provision of four basic values; justice, autonomy, non-maleficence, and beneficence (32). These principles derive the fact that any AI system should be riskless, reliable, accurate, and unfailing. Furthermore, legislative reforms to interject supportive amendments in the existing laws must perpetuate the assurance of data protection and data usage within the boundaries of the patient's consent.

Data ethics is the novel field that is essentially concerned with the evaluation of moral problems associated with data, algorithms, and related practices (33). Privacy, informed consent, ownership, objectivity, and 'big data divide' are five major areas of concern in terms of data ethics and when they are not properly protected, they become five central areas of infringement (34). Multiple violations may strike the privacy of patient data if the balance between personal information and advancing artificial intelligence is not maintained (35). To avoid such breaches, radiology should focus on an important aspect of data ethics which is the 'Ethics of practices'. Ethical AI practices should be defined and documented to ensure the promotion of technical growth while still maintaining patient consent, user privacy, and use of secondary data (35).

A sense of responsibility is always associated with the act of making a decision. Hence, in the case of any harm, the human being responsible for the action holds accountability but an ethical question arises when decisions or actions that resulted in harm are ascribed to the use of AI technologies. To delve deeper into the attribution of accountability, in the case of harm caused by an AI system, it is important to look into Aristotle's ethics. Two traditional conditions attributed to attainment of responsibility have been described since Aristotle; the control condition (also called the freedom condition), inferring if one could be exempt for an act owing to the lack of freedom, and the epistemic condition (also referred to as the knowledge condition) (36). Full responsibility is only attributed when the epistemic condition is fulfilled along with the control condition. The control condition holds you responsible for an act only if it is committed by you, but the epistemic condition makes it necessary for someone to know the nature of the act to be held fully accountable for it (36). The AI does not meet the traditional Aristotelian conditions for full moral responsibility (37). Therefore, it only makes sense if the AI is not expected to act voluntarily since it is not conscious of what it is doing. This assumption also leaves behind only the radiologist to be attributed to the responsibility of harm.

Furthermore, the unanswered ambiguity of including CAD results in the patient's radiological report and complete disclosure of the information that the diagnosis is supported by an AI system is still under debate. Additionally, bound by the limitations of the human body, there are certain features on images that the radiologist cannot quantify. For instance, textural analysis can generate numerous features that are undetectable and unquantifiable by a human being. Therefore, if the radiologist is required to validate the output of an AI system, they will potentially be exposed to the risk of validating the unknown (36). Another major aspect that could potentially lead to gaps in the provision of excellent patient care is the risk of automation bias. Automation bias is the proclivity of the human mind to accept suggestions generated by an automated program and ignore non-automated contradictory information, even if it is correct. Unfortunately, the risk of automation bias also exists in the field of radiology (38). The AI designers should be mindful of the fact that a high degree of automation without maintaining the reliability of the systems could drastically result in numerous negative impacts and impeding completely the operators' decision-making process could even prove to be deadly (39).

The extensive use of AI in the field of radiology may potentially result in the reduced motivation of younger doctors to incorporate themselves in this field. It may also result in fewer training opportunities since the same workload could be successfully met in a shorter amount of time by an AI system which reduces the need for radiologists. This message resonates with everyone associated with the healthcare profession. A survey conducted in 17 Canadian medical schools concluded that 67.7% of medical students agreed that AI would reduce the demand for radiologists, a minority (29.3%) believed that AI would replace radiology, and considering radiology as a career choice, in these times of automation, caused anxiety among 48.6% of the students (40). This raises many more ethical questions related to the potential unemployment of many aspiring radiologists and professionals associated with the field of medical imaging.

WHERE ARE WE HEADED?

The utilization of computing technologies to the benefit of a profession is indispensable for the attainment of modernity, and the field of diagnostic imaging has always had a close traditional association with the newer, finer, and superior computing machinery. The role of the computer was drastically dilated in the field of radiology in the 1970s after being initially introduced in the 1960s. Although it was an expansive step towards the future, the use of computers was still limited to administrative tasks only. The earliest use of computers for imaging was reported first in the nuclear medicine digital subtraction angiography (41). CT in the 1970s and MRI in the 1980s were the next major adaptations of computing technology in radiology (41). This historical analysis indicates that the field of radiology will continue to incorporate newer technology in the future as well but questions like 'Will AI entirely replace the field of radiology?' raise various suspicions in the minds of resident physicians as well as medical students (42). However, it is clear that AI technologies only serve a supplemental purpose therefore, are often more appropriately and conveniently approved as augmentation equipment rather than replacement tools (42, 43). Neverthe-

less, some people associated with the healthcare profession predict a complete replacement would take part and this prediction instills a sense of anxiety (40). Such a poor prognosis of this field results from the gross lack of education regarding AI. A survey conducted to understand the impact of the rise of AI in radiology concluded that 73.3% of the radiologists estimated that they had received insufficient knowledge regarding AI but an estimated 94.4% were willing to attend continuous medical education in this field (44). This proves that radiologists are open to accepting such changes when educated in the relative field.

Moreover, a recent survey has indicated that AI will outperform humans in many activities including the performance of surgeries (45). The experts also believed in the high likelihood of AI surpassing humans in the next 45 years (45). Therefore, a sense of employment insecurity due to a fear of complete replacement has taken over the radiologists. Yet, the trend recently has shifted from a sense of complete replacement to the notion that AI will not replace the radiologists, but rather that the radiologists who use AI will replace those that do not. Hence, indicating that radiologists will have to keep up with the advancements in order to have a sense of security in their field.

Moreover, the potential uses of deep learning models in the training of residents and general radiologists cannot be overlooked. The images labeled by specialists can be of immense utility to instill confidence in the young radiologists by training them for the recognition of difficult diagnoses. Furthermore, AI technology can be used as a tool to alert radiologists towards patients that require urgent care. It also finds potential in decreasing a radiologist's daily workload, which would increase the optimization of the workforce (46).

Considering all of these aspects, it can be safely stated that the eagerness associated with the future of AI should be met with appropriate planning. However, the potential of AI, although vast, should not be over-glorified. Since an AI system is trained in only one aspect, it cannot make associations about context, and hence, it is unlikely that AI will completely replace radiologists (47). Even further, it has the potential to broaden the scope of the radiologists' work by connecting them with technology and becoming a source of superior tools.

CONCLUSION

The development of potent algorithms has indicated promising outcomes in the future. It appears that AI not only finds applications in radiology, but has the potential to revolutionize other fields of medicine and surgery as well. However, the fast-growing world of AI also demands the upgradation of the code of ethics. Under no circumstances should the ethical obstacles be overshadowed by the complications faced during the development of AI systems. The ethical code should also be reformed with each development in automation technology, and the opinions of radiologists and AI engineers should be incorporated to ensure the formation of an all-inclusive code of ethics; the goal of which is to direct physicians towards the best possible outcome for the patients. Recognizing these weaknesses and challenges as potential threats for disseminating AI systems and devising policies for the regulation of technological expansion, maintenance of quality, and protection of patient data will surely help highlight the promising future of interdisciplinary uses of AI.

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FEAR OF COVID-19 AMONG MEDICAL STUDENTS AND ASSOCIATED FACTORS

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ABSTRACT

Aims: To determine the level of COVID-19 fear among Turkish medical students, and show the relationship the types of education (online, hybrid, face to face), age, gender, grade, and level of fear. ***Methods:*** The study was conducted with 536 medical students from 30 different universities in Turkey. The questionnaire comprised 1 open-ended and 6 multiple choice questions for assessment of the demographic structure, in addition to 7 Likert-type questions within the 'Fear of COVID-19 Scale'. ***Results:*** Participants comprised 352 (65.7%) female and 184 (34.3%) male students, with a mean age of 20.04 ± 2.59 years and they showed significantly different Fear of COVID-19 Scale scores with regard to gender. The past or current presence of COVID-19 was determined as another variable that created a significant difference in the Fear of COVID-19 Scale scores. However, no relation between the past or current presence of COVID-19 in a family member and the Fear of COVID-19 Scale scores were found. ***Conclusion:*** In this study, it is demonstrated that fear of COVID-19 is higher among females and non-infected medical students compared to males and infected ones, respectively. These results can be used in assessing the fear level of COVID-19 among medical students concerning their gender their gender and infection history. ***Keywords:*** COVID-19, medical students, fear, distance education, medical education

INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic, with its relatively high mortality and rapid transmission, has caused a huge burden to governments, organizations, and individuals worldwide (1,2). According to the World Health Organization's weekly reports, there have been over 75 million cases and over 1.6 million deaths since the beginning of the pandemic, December 20th. The United States of America, Brazil, and Turkey were the countries reporting the highest numbers of new cases on December 14-20, 2020 according to the same reports (3).

Public health precautions such as quarantine, social distancing, and school closures are implemented all around the world to keep the spread of COVID-19 under control (4). As a part of these precautions, on March 10, 2020, the Turkish Ministry of Education announced that face-to-face education would be suspended for 3 weeks starting from March 16, 2020. Since then, distance education has been introduced throughout the country remaining the most common type of education today (5).

Since medical schools educations are mostly practical, it was later on authorized by the Council of Higher Education making the decision of calling their students to in person instructions. Following that, some schools remained in lock down, some were reopened, and some started a hybrid (a mix of online and in-person learning) education. Today, the types of medical education in Turkey still vary between online and face-to-face, depending on the school and grade level.

Studies show that anxiety, fear, worry, and depression are psychological effects on university students during public health emergencies (6-8). Li et al. (7) reported that the mental health of university students have been affected during the pandemic. In another study conducted by Cao et al. (8), it has been shown that about 24.9% of college students have experienced anxiety because of the COVID-19 pandemic.

There are many scales associated with COVID-19 and the Fear of COVID-19 Scale (FCV-19S) developed by Ahorsu et al. (9) is one of them. FCV-19S is a 7-item, 5-point Likert scale. Ladikli et al. (10) reported that the FCV-19S can be used in the Turkish population as a reliable and valid measurement tool. In this study, we aimed to determine the level of COVID-19 fear among Turkish medical students and show its relationship with the type of education, age, gender, and grade.

MATERIAL AND METHODS

This cross-sectional study was approved by the Scientific Research Ethics Committee of Trakya University, School of Medicine (Protocol Code: TÜTF-BAEK 2020/440). In this study, a Turkish version of FCV-19S prepared by Ladikli et al. (10) and a questionnaire consisting of 7 questions were gathered in a single Google Form. The link to the form was shared via various social media channels and online chat groups of medical schools to reach medical students.

A paragraph to inform participants and get consent was added to the beginning of the form. Sociodemographic information, participants' current education type, and the current or past presence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection among the participants and their families were ques-

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tioned. FCV-19S was added as the last part of the form. FCV-19S is a scale consisting of seven questions. On this scale each question is scored between 1-5 points, and the total score is ranged between 7-35 points. The overall questionnaire is shown in Table 1. Answering all questions was mandatory to save the form. Logging in with a Google account was also mandatory to ensure every participant sent only one answer.

Data were analyzed with RStudio version 4.0.2. Numbers and percentages were stated for a clear declaration of answers. Moreover, calculations of means and standard deviations were used to express the results more concisely. The relationship between variables was analyzed using Welch's t-test and one-way ANOVA. A p value of <0.05 was evaluated as statistically significant.

Table 1: The questionnaire used in the study.

Questions	*Answers*
What is your age?	
What is your gender?	Female / Male
Which university do you study at?	
Which grade are you in?	1 / 2 / 3 / 4 / 5 / 6
Have you been infected by SARS-CoV-2?	Yes / No
Has someone in your family been infected with SARS-CoV-2?	Yes / No
What is your current education type?	Online / Hybrid / Face-to-face

RESULTS

This study was conducted among 536 medical students from all grade levels of medical school. The sample comprised of 352 (65.7%) female participants and 184 (34.3%) male participants, with a mean age of 20.04± 2.59 years. The number of participants who had been infected by SARS-CoV-2 was 53 (9.9%), whereas 483 (90.1%) of the participants had not been diagnosed with COVID-19. In addition to the infection status of the participants, the presence of a diagnosed COVID-19 patient among the family members of the participants was questioned. One hundred and sixty (29.9%) participants had at least one family member who had been diagnosed with COVID-19, whereas, 376 (70.1%) of the participants had no family member diagnosed with COVID-19. Distribution of demographic data are shown in Table 2.

The mean score for the questions on the scale was 17.1 (SD: 5.76, range: 7-35 points). Female participants had a mean score of 18.33 (SD: 5.59, range: 7-35 points), male participants had a mean score of 14.73 (SD: 5.33, range: 7-35 points), indicating a statistically significant difference between the scores of females and males (p= 1.609.10-12). The FCV-19S questions and the distribution of the Likert-type answers are shown in Table 3.

The sample group of students was from 30 different universities geographically distributed all over Turkey, where more than half of the participants were from universities located in Marmara region. Five-hundred ten (95.1%) students indicated that they had a completely online education at the time they participated in the study. 17 (3.2%) participants indicated that their current education type is hybrid (both online and face-to-face), and 9 (1.7%) participants declared that their current education is completely face-to-face. However, there was no significant impact of the education type on the level of COVID-19 fear (p= 0.5905). In addition, no statistically significant difference was observed between the FCV-19S scores of participants from different grade levels of medical school (p= 0.11857).

There was a statistically significant difference between the FCV-19S scores of previously infected and non-infected participants (p= 0.026). While non-infected participants had a mean score of 17.27 (SD: 5.80), infected participants had a mean score of 15.57 (SD: 5.09). When the participants were grouped according to the presence of an infected family member, there was no statistically significant difference between the two groups (p= 0.9978).

Table 2: Distribution of the demographic data.

Variables	*Number of Students [n (%)]*	*P-value**
Age		
17-19	271 (50.6)	
20-22	217 (40.5)	
23-25	42 (7.9)	
25+	5 (1.0)	
Gender		***1.609.10-12***
Female	352 (65.7)	
Male	184 (34.3)	
Academic year		0.11857
1st year	259 (48.3)	
2nd year	75 (14.0)	
3rd year	102 (19.0)	
4th year	40 (7.5)	
5th year	52 (9.7)	
6th year	8 (1.5)	
Education type		0.590516
Online	510 (95.1)	
Hybrid	17 (3.2)	
Face-to-face	9 (1.7)	
Presence or history of SARS-CoV-2 infection in the participant		***0.02601***
Yes	53 (9.9)	
No	483 (90.1)	
Presence or history of SARS-CoV-2 infection in the participant's family		0.9978
Yes	160 (29.9)	
No	376 (70.1)	

*Statistically significant values are marked as bold.

DISCUSSION

Following the report of first COVID-19 case in Turkey on March 11, 2020, education was suspended for 3 weeks. Soon it was realized that to overcome the spread of virus, a nationwide lockdown could be necessary. Therefore, almost all universities in Turkey switched to online education, medical schools included. Contrary to expectations, COVID-19 cases continued increasing, though there were relatively fewer cases during the summer months (11). Consequently, the Council of Higher Education in Turkey suggested that universities continue their online education throughout the fall semester of 2020. Although, some universities preferred hybrid or face-to-face education most medical schools in Turkey provided educational services to their students online. The purpose of this study is to determine if there is a relation between

Table 3: Questions of the Fear of COVID-19 Scale and the prevalence of the answers.

Fear of Corona Items	*Strongly disagree [n (%)]*	*Disagree [n (%)]*	*Neutral [n (%)]*	*Agree [n (%)]*	*Strongly agree [n (%)]*	*Cumulative score [n (mean)]*
I am most afraid of Corona.	56 (10.4)	134 (25.0)	137 (25.6)	156 (29.1)	53 (9.9)	1624 (3.0)
It makes me uncomfortable to think about Corona.	68 (12.7)	124 (23.1)	78 (14.6)	190 (35.4)	76 (14.1)	1690 (3.1)
My hands become clammy when I think about Corona.	280 (52.2)	193 (36.0)	42 (7.8)	11 (2.1)	10 (1.9)	886 (1.7)
I am afraid to lose my life because of Corona.	122 (22.8)	140 (26.1)	102 (19.0)	124 (23.1)	48 (9.0)	1444 (2.7)
When I read news and stories about Corona on social media, I become nervous or anxious.	83 (15.5)	119 (22.2)	111 (20.7)	162 (30.2)	61 (11.4)	1607 (2.9)
I cannot sleep because I worry I am going to get Corona.	331 (61.8)	156 (29.1)	31 (5.9)	11 (2.1)	7 (1.3)	815 (1.5)
My heart races or palpitates when I think about getting Corona.	228 (42.5)	160 (29.9)	70 (13.1)	49 (9.1)	29 (5.4)	1099 (2.0)
			Cumulative Score of the Scale			***9165 (17.1)***

the levels of COVID-19 fear and the type of education methods (online, hybrid, face-to-face).

In our study, there was a significant difference between female and male students regarding FCV-19S scores, indicating higher scores in females. This result is consistent with a study carried out by Nguyen et al. (1) among Vietnamese medical students, which determined that being male has a significant negative association with fear of COVID-19. On the other hand, Ahorsu et al. (9), who developed the FCV-19S scale, found that gender and fear of COVID-19 have no apparent relation in a study of the general population in Iran. However, in a corresponding study carried out by Haktanir et al. (12) among the general population in Turkey, FCV-19S scores were reported to be higher among women. Anxiety-related disorders are known to occur more frequently in females than males (13).Our findings are in line with this general trend in anxiety.

In the present study, there was a considerable difference found between FCV-19S scores in previously infected and non-infected participants where previously infected participants had a lower mean score. Knowing that age is a determining factor how a person will undergo the illness, level of seriousness approaching the pandemic could've been affected in students who already had COVID-19. Furthermore, when the participants are analyzed according to the presence of an infected family member, no statistically significant difference in FCV-19S scores between these two groups were found. We do not have a strong argument that could explain this latter behaviour of the participants. As far as we are aware of the current literature on COVID-19, these two last aspects have not been assessed in any other studies.

Our data of FCV-19S scores between different age groups of students shows that there is no remarkable relation between the levels of COVID-19 fear and participants' age. In the present study, the majority of the participating students were first, second, and third graders, which amounted to 81.3% of all participants. Therefore, the study may not differentiate the level of COVID-19 fear between low and higher graders because of the insufficient number of higher-grade students. However, in a study conducted by Martinez-Lorca et al. (15) about the fear of COVID-19, among the university student population in Spain including medical students, a significant relationship between age and FCV-19S scores has been reported. In the same study, it is stated that first-year students presented a higher level of FCV-19S score than the students of other grades. Another study by Nguyen et al. (1) concluded that older medical students (23-26 years of age) were affected less than younger medical students according to their FVC-19S scores.

Our study found no statistically significant relationship between the type of education and levels of COVID-19 fear. This may be due to the fact that almost all students (95.1%) that took part in our study were participating in fully online education. If our survey had included enough participants that took part in face-to-face education the results might reflect the difference. To the best of our knowledge, there is no study in the literature that assesses this relation.

Our study has several limitations. First, the present study did not have any means to measure if participants already had any psychological disorders (e.g. anxiety or depression). This may have affected the sensitivity and specificity of our survey results. Second, the present survey is carried out among the medical students to whom we may reach relatively easily by social media instruments. Therefore, the study necessarily excludes the students who could not be reached by such means. As an example, the number of sixth-graders who mostly have face-to-face education that participated in the survey is not enough to conclude their levels of COVID-19 fear. This prevents an adequate generalization of our findings to the whole body of medical students. The lack of relationship between age and FCV-19S scores may be due to this fact. More studies are required to address the aforementioned limitations.

In conclusion, our study demonstrated that the fear of COVID-19 is higher among females and non-infected medical students compared to males and infected students, respectively. These results can be used in assessing the level of COVID-19 fear among medical students regarding their gender and infection history. Further studies are needed including students of all ages and grades to overcome the limitations imposed by convenient sampling.

Ethics Committee Approval: This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2020/440).
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RETROSPECTIVE ANALYSIS OF THE IMPACTS OF TREATMENT REGIMENS ON THE PROGRESSION AND PROGNOSIS OF DIABETIC RETINOPATHY AND VISUAL ACUITY IN TRAKYA UNIVERSITY SCHOOL OF MEDICINE

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ABSTRACT

Aims: To retrospectively analyze the impacts of treatment regimens on progression and prognosis of diabetic retinopathy and visual acuity in Trakya University Hospital. ***Methods:*** This retrospective cross-sectional study was conducted with patients who were diagnosed with diabetic retinopathy in the Ophthalmology Department of Trakya University Hospital between January 2006 and January 2020. ***Results:*** Initially, 798 eyes from 399 patients diagnosed with diabetic retinopathy met the inclusion criteria. Non-proliferative diabetic retinopathy was present on 202 (50.6%) patients, and 197 (49.4%) patients had proliferative diabetic retinopathy. Twenty-five patients (6.2%) had proliferative diabetic retinopathy progression. Patients with proliferative diabetic retinopathy progression had no difference in terms of cataract surgery, gender, and hypertension existence than the ones who did not experience proliferative diabetic retinopathy progression. There was no relation between stability, increase or decrease of visual acuity, the type of diabetes, retinal laser photocoagulation treatment, and the type of intravitreal injection. ***Conclusion:*** Our study showed that retinal laser photocoagulation treatment and cataract surgery had no significant impact on visual acuity prognosis, unlike the initial examination visual acuity values. Additionally, it was also shown that the different types of intravitreal injections made no dissimilar results on visual acuities. In addition, in our study, it was revealed that gender, presence of hypertension, and cataract surgery may not have a significant relation with proliferative diabetic retinopathy progression. Further studies are needed to thoroughly reveal the relation between the treatment regimens, progression, and prognosis of the disease. ***Keywords:*** Diabetes mellitus, diabetic retinopathy, epidemiology, macular edema

INTRODUCTION

Diabetic retinopathy (DR) is the most common cause of preventable blindness in the working-age population in developing countries (1). DR is a specific microvascular complication of diabetes at early stages (1). Presently, the global prevalence of DR goes up to 34.6%, meaning that it could occur in a third of the people with diabetes and is associated with an increased risk of life-threatening systemic complications including coronary heart disease, heart failure, nephropathy, and stroke (2). The prevalence hits even higher ratios, around 40.3%, in developed countries (2). Thus, 3.6% of patients with type 1 diabetes mellitus (DM) and 1.6% of patients with type 2 DM are estimated to become blind at further stages (2).

Diabetic retinopathy is graded clinically in most of the ophthalmology centers and the grading remains to be based on the original Early Treatment Diabetic Retinopathy Study (ETDRS) grading scheme, including mild and moderate non-proliferative diabetic retinopathy (NPDR), severe NPDR (pre-proliferative diabetic retinopathy), non-high-risk proliferative diabetic retinopathy (PDR), and high-risk PDR (3). The presence of diabetes for 20 years causes retinopathy in about 80% of the patients (4). DR causes microaneurysms, appearing as tiny red dots which represent small capillary aneurysms and bulges. These aneurysms are abnormally permeable but not harmful by themselves. Permeability increase leads to yellow-white discrete patches called hard exudates to form on the retina in a ring around the leaking capillaries. The progression of hard exudates on the macula gradually causes vision loss and eventually leads to blindness. In PDR, ischemia of the retina predisposes to the development of new vessels with dangerous formation. New peripheral vessels are less likely to cause vitreous hemorrhage than the ones on the disc, which are commonly known to bleed and cause preretinal hemorrhages resulting in blindness due to vitreous hemorrhage (3).

Routine fundus examination should be performed on all diabetic patients (4). A screening modality for DR is recommended to be performed with dilated slit-lamp biomicroscopy with a lens or dilated fundoscopy containing a stereoscopic examination of the posterior pole. New technologies such as digital cameras and teleophthalmology provide improved results in screening (5). Optimal control of blood glucose, blood lipids, and blood pressure plays a humongous role in the risk reduction of retinopathy development and progression (1). Intravitreal injections, panretinal photocoagulation (PRP) and vitrectomy are the interventional approaches in order to manage the complications of DR. Anti-VEGF therapy are recommended as a stand-alone treatment or in combination with PRP. While studies of anti-intravitreal anti-VEGF injections in the

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treatment of DR are promising, this approach is not yet considered standard. In addition, the difference in effects between different types of intravitreal anti-VEGF injections is still under debate and being studied (4). Recognizing the patients with DR at the early stages provides better visual acuity results. Therefore, it is quite important to check up on patients regularly for DR and know the potential complications of the disease for better patient management.

The aim of this study is to retrospectively analyze the impacts of treatment regimens on prognosis and progression of diabetic retinopathy and visual acuity in a tertiary clinic in the Thrace region in Turkey.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TUTF-BAEK 2020/426). This retrospective cross-sectional study analyzed patients who were diagnosed with DR in the Ophthalmology Department of Trakya University Hospital between January 2006 and January 2020. The study was carried out in accordance with the tenets of the Declaration of Helsinki. Written informed consent for the use of medical information of patients was received from all of the participants.

Demographic data such as age and gender, accompanying systemic comorbidities (such as hypertension, diabetic nephropathy), the type of diabetes mellitus (type 1 or type 2), the usage of oral anti-diabetic agents or insulin injection, and initial and following clinical findings were obtained from the medical records of the patients. All patients underwent a complete ophthalmologic examination at each visit including best-corrected visual acuity (BCVA) determined by Snellen chart, anterior segment biomicroscopic examination, intraocular pressure (IOP) measurement with Goldmann applanation tonometer, and detailed fundus examination obtained with 78-diopters non-contact lens.

The following findings were documented at the initial visit: type of DR (non-proliferative or proliferative), lens status (phakic, pseudophakic, or aphakic), presence of macular edema, and presence of glaucoma. DR classification was made based on the criteria determined by the ETDRS (4).

The following findings were documented at the follow-up visits: the presence of intravitreal injection, number of injections, the progression of DR from non-proliferative to proliferative, the presence of PRP, and the presence of surgical interventions (cataract surgery or vitreoretinal surgery).

Patients who were diagnosed with DR are included. DR patients who have poorer visual acuity than positive light perception, on-set corneal pathologies, ocular-vascular diseases, and macular pathologies that could be unreliable for fundi examination were excluded from this retrospective study.

In this retrospective study, treatment data such as the presence of cataract or/and vitrectomy surgeries, appliance, and the type of intravitreal anti-VEGF injections, medical treatment regimens for diabetes mellitus; and examinational findings such as BCVA, IOP, examinational fundi findings such as the presence of macular edema, intravitreal hemorrhage, type of on-set DR during follow-ups were statistically tested to reveal the clinical impacts on progression and prognosis of diabetic retinopathy and visual acuity.

Statistical Analysis

The collected data were analyzed statistically by using the SPSS version 20 for Windows. Mean and standard deviation values were calculated using descriptive statistical measures. The frequency distribution of qualitative data was quantified in percentages. The Chi-square test was used for qualitative comparison. The normality distribution of the data was evaluated with the One-sample Kolmogorov-Smirnov test. Quantitative data were compared with the Independent Sample t-test. P-value of <0.05 was considered to be statistically significant.

RESULTS

Initially, 798 eyes from 399 patients with the diagnosis of DR met the inclusion criteria of having visual acuity results greater than positive light perception and above, absence of corneal pathologies, ocular-vascular diseases (central retinal artery occlusion, retinal venous occlusion), accompanying macular pathologies like macular hole and macular degeneration. Two hundred and thirty-two (58.4%) patients were female, and 166 (41.6%) patients were male. The summary of patients' characteristics (age, mean duration of follow-up, gender, type of DM, comorbidity, and DM treatment) is presented in Table 1. Six (1.5%) patients had diabetic nephropathy at the first admission to the clinic.

Table 1: Patients' characteristics.

	Number of Patients [n (%)]
Age (years)*	63.5 ± 9.1 (31-85)
Duration of follow-up (years)*	5.7 ± 3.5 (1-14)
Gender	
Female	232 (58.4)
Male	167 (41.6)
Type of DM	
Type 1	12 (3)
Type 2	387 (96.5)
Comorbidity	
Hypertension	213 (53.4)
Hyperlipidemia	6 (1.5)
Renal disease	3 (0.7)
Cardiac disease	65 (16.2)
Pulmonary disease	5 (1.2)
None	107 (26.8)
Treatment of DM	
OAD	130 (32.6)
Insulin	129 (32.3)
OAD + Insulin	109 (27.3)
None	31 (7.8)

DM: *Diabetes Mellitus,* ***OAD:*** *Oral anti-diabetic*
*Data were expressed as mean ± SD (min-max).

Initial visual acuities were 0.32 ± 0.37 LogMAR units (range; from 3 to 0 LogMAR units) in the right eyes and 0.32 ± 0.36 LogMAR units (range; from 3 to 0 LogMAR units) in the left eyes. Three hundred and nine (77.4%) patients were phakic, 90 (22.6%) patients were pseudophakic, and 238 (59.6%) patients had cataracts. Twenty-one (5.3%) patients had rubeosis iridis. The mean intraocular pressure was 16.1 ± 4.3 mmHg (range; from 7 to 56 mmHg) in the right eyes and 16.2 ± 4.1 mmHg (range; from 8 to 50 mmHg) in the left eyes. Forty-two (12.5%) patients had glaucoma at the initial examination. First ophthalmologic examinational

Table 2: Outcomes of patients.

	Initial		*Final*	
	Right Eye	***Left Eye***	***Right Eye***	***Eye***
BCVA (LogMAR Unit)	0.32± 0.37	0.32 ± 0.36	0.41 ± 0.39	0.4 ± 0.38
IOP (mmHg)*	16.1 ± 4.3 (7 - 56)	16.2 ± 4.1 (8 - 50)	-	-
CMT (µm)	323 ± 117.5 (18 - 748)	336.5 ± 131.4 (23 - 763)	290.1 ± 121.3 (17 - 801)	291.1 ± 128.1 (8 - 921)
Stage of Retinopathy [n (%)]				
NPDR	202 (50.6)			
PDR	197 (49.4)			
Macular Edema* [n (%)]				
Present	182 (45.6)			
Absent	217 (54.4)			
Lens Statement [n (%)]				
Phakic	309 (77.4)			
Pseudophakic	90 (22.6)			
Intravitreal Hemorrhage* [n (%)]				
Present	93 (23.3)			
Absent	306 (76.7)			

Mean ± SD (min – max); n (%)
***BCVA:** Best corrected visual acuity, **IOP:** Intraocular pressure, **CMT:** Central macular thickness*
**The data presented here were obtained only from the initial examinations.*

data (BCVA values, intraocular pressures (IOPs), mean macular thickness, number of patients with NPDR or PDR, macular edema presence, lens statement, and intravitreal hemorrhage presence) are presented in Table 2.

Phacoemulsification cataract surgery was performed on 136 (34.1%) patients and vitrectomy on 63 (15.8%) patients due to tractional retinal detachment, resistant macular edema, and intravitreous hemorrhage. PRP was performed on 278 (69.7%) patients in order to treat PDR and ischemic pathologies. Sixty-seven (16.8%) patients had intravitreal aflibercept injection, 117 (29.3%) patients had intravitreal ranibizumab injection, 66 (16.5%) patients had intravitreal dexamethasone implant, and 71 (17.8%) patients had intravitreal bevacizumab injection by the reason of diabetic macular edema. Twenty-five (6.2%) patients had a progression from NPDR to PDR. The mean progression duration was 37.6 ± 43.1 months (range; from 3 months to 168 months). Patients with PDR progression had no statistically significant difference in terms of cataract surgery, gender, and hypertension existence than the ones who did not experience PDR progression (p=0.146, p=0.802, p=0.272, respectively). On the latest examination, the mean visual acuity value was 0.41 ± 0.39 LogMAR units (range; from 3 to 0 LogMAR units) in the right eyes and 0.4 ± 0.38 LogMAR units (range; from 3 to 0 LogMAR units) in the left eyes. One hundred and sixty-five (20.7%) eyes were stable on visual acuity. Two hundred and fifty-two (31.6%) eyes had an increase in visual acuity by time whereas 381 (47.7%) eyes were observed to have a decrease. There was a strong positive correlation in visual acuity between the latest and initial examinations (r= 0.445, p < 0.001). Eventually, we concluded that there was no statistically significant relationship between stability, increase or decrease of visual acuity and the type of diabetes, retinal laser photocoagulation treatment, and the type of intravitreal injection (p= 0.967, p= 0.333, p= 0.132, respectively) (Table 2 and 3).

Table 3: Outcomes of patients.

	Number of Patients [n (%)]
PRP	
Yes	278 (69.7)
No	121 (30.3)
Type of Intravitreal Injection	
Aflibercept	67 (16.8)
Bevacizumab	71 (17.8)
Ranibizumab	117 (29.3)
Dexamethasone	66 (16.5)
None	78 (19.5)
Surgery	
Phacoemulsification	136 (34.1)
Vitrectomy	63 (15.8)
None	200 (50.1)

***PRP:** Panretinal Photocoagulation*

DISCUSSION

Diabetic retinopathy has been known to be a microvascular disease for a long time. Earlier population-based studies have revealed that almost all individuals who have type 1 diabetes and more than 60% of the ones with type 2 diabetes come across the development of DR in the first 2 decades of the disease (6, 7). Type 2 diabetes is expected to increase in prevalence since sedentary lifestyles and obesity have become more common, which would result in more individuals with DR (6, 8).

Diabetic retinopathy more commonly occurs in elderly individuals with diabetes. In our study, it was revealed that the mean

age of patients with type 1 diabetes was 51.3 years and the mean age of patients with type 2 diabetes was 63.8 years, which are quite similar to other studies (9, 10). Regarding gender, the number of female patients (58.4%) was slightly more than males in our study. However, in most studies, the number of male and female patients was similar (9, 11-15). These demographic data are important for the different clinical approaches in daily practice.

Previous studies have shown that DR is asymptomatic at early stages, and visual impairments only develop due to PDR or advanced macular disease. Therefore, patients with DR should regularly undergo complete ophthalmologic examinations including BCVA, anterior segment biomicroscopic examination, IOP measurement, and detailed fundus examination for better management of the disease (3, 16). In the present study, patients had visual impairments at the initial examination, whereas in other studies patients at the early stages had decent visual acuities (17, 18). IOPs were found to be in the normal range. The number of patients with NPDR was greater than the ones with PDR. According to other studies, approximately 27.5% of the individuals with DR have diabetic macular edema (19, 20). It has been seen that 45.6% of patients had diabetic macular edema at the first admission. The difference between the results of initial visual acuities could be attributed to the poor attendance of patients to ophthalmological appointments alongside the differences of genetic and environmental factors.

The stage of DR severity primarily affects the tendency of pr gression to vision-threatening PDR. The ETDRS has shown that the possibility of progression to PDR from severe NPDR is approximately 52% in 1 year (21). Recent studies have revealed various rates of PDR progression from baseline DR, ranging from 5.3% to 11.0% (22, 23). Our results of PDR progression from NPDR (6.2%) align our findings with most of the recent studies. The primary cause of chronic renal disease has been known to be diabetic nephropathy, accounting for 40% of total annual new cases of end-stage renal disease development. Albuminuria, progressive glomerular filtration rate decline, and blood pressure elevation are the complications of diabetic nephropathy. These complications of diabetic nephropathy have been revealed to be important independent predictors of PDR progression. As for DR, the major risk factors for diabetic nephropathy were identified to be prolonged duration of diabetes, hypertension, and poor glycemic control. In addition, proteinuria or being on dialysis increase the risk of vision-threatening PDR. In the present study, there were not enough patients with nephropathy to evaluate the relationship between nephropathy and PDR progression. We have found that cataract surgery, gender, and the presence of hypertension had no statistically significant impact on PDR progression, which is supported by other studies (21, 24).

Diabetic retinopathy can cause changes in blood vessels, microaneurysms, hemorrhages, exudates, and retinal thickening. Any advanced pathologies of DR on the macula can lead to visual loss. Peripheral retinal laser photocoagulation is performed to reduce the risk of advanced vision impairments. It is still unknown if any type of laser treatment is superior to another. Focal macular laser photocoagulation is performed in order to reduce the risk of moderate visual impairment in patients with clinically severe macular edema and mild to moderate NPDR. Grid photocoagulation performed to the zones of the thickened retina can improve visual acuity. However, studies have shown that the photocoagulation treatment is unlikely to remain beneficial on patients with maculopathy but is helpful on clinically significant macular edema. Intravitreal triamcinolone acetonide was applied to patients with macular edema who were resistant to the previous macular laser photocoagulation treatments. This was done to provide improved visual acuity and reduced macular thickness; however, repeated injections were required to maintain beneficial features. Common complications of intravitreal triamcinolone are the progression of cataract and secondary ocular hypertension; infectious endophthalmitis complication is rare. Intravitreal anti-VEGF injections are performed to reduce the macular thickness and improve visual acuities. Repeated injections are also needed to maintain beneficial features (25). In our clinic, patients with PDR and ischemic pathologies had panretinal laser photocoagulation treatment and had intravitreal injections with the purpose of macular edema medication. According to the results of the study of Baker et al. (26), aflibercept is superior to bevacizumab and ranibizumab in eyes with moderate to severe visual impairments but neither panretinal laser photocoagulation nor any kind of anti-VEGF injection has a statistically significant difference in eyes with mild visual impairments. The prognosis of visual acuities is associated with various factors like the severity of retinopathy and HbA1c management. In the study of Bressler et al. (27), it was revealed that panretinal laser photocoagulation had less impact on the improvement in visual acuities in eyes with severe retinopathy or higher HbA1c, compared with the eyes with less severe retinopathy or lower HbA1c. Our results have shown that the type of diabetes, retinal laser photocoagulation, and the type of intravitreal injection have no significant impact on visual acuity. Vitrectomy can help to reduce visual loss if performed early in patients with intravitreal hemorrhage, especially in ones with PDR (27). Patients with DR in our clinic underwent cataract surgery and vitrectomy for the reason of tractional retinal detachment, resistant macular edema, and intravitreal hemorrhage.

The main limitations in our study were the lack of data in HbA1c values of the patients throughout follow-ups and the poor number of DR patients with nephropathy to investigate further impacts on the prognosis of the disease. Diabetic nephropathy and HbA1c values are known to be considerably related to PDR progression from NPDR, have a strong impact on the prognosis of visual acuity and, highly important in managing the complications of DR (21-23).

In conclusion, DR happens to be a common and feared vision-threatening microvascular disease despite the increased treatment availability for the disease. With the global rise in the number of diabetic individuals, the number of people at the risk of DR is likely to increase considerably. Early diagnosis, check-ups, and proper treatment are the crucial points of DR management. Retinal laser photocoagulation treatment and intravitreal anti-VEGF injections are significantly useful for neovascularization, ischemic pathology, and macular edema treatment. As our study showed, retinal laser photocoagulation treatment and cataract surgery had no significant impact on visual acuity prognosis unlike the initial examination visual acuity values. In addition, the results have also revealed that the difference between the types of intravitreal injections made no dissimilar end-results on the prognosis of visual acuities. Furthermore, it was revealed that gender, hypertension presence, and cataract surgery may not have a significant relationship with PDR progression. Further studies are needed to thoroughly reveal the relationship between treatment regimens and the progression and prognosis of the disease.

Ethics Committee Approval: This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TUTF-BAEK2020/339). ***Informed Consent:*** Informed consent was obtained from all subjects. ***Conflict of Interest:*** The authors declared no conflict of interest. ***Author contributions:*** Concept: MÖİ, RG. Supervision: MÖİ, RG. Resources: MÖİ, RG. Materials: MÖİ, RG. Data collection and/or processing: MÖİ, RG. Analysis and/or Interpretation: MÖİ, RG. Literature Search: MÖİ, RG. Writing Manuscript: MÖİ, RG. Critical Review: MÖİ, RG. ***Financial disclosure:*** The authors declared that this study received no financial support.

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EVALUATION OF TOILET HABITS AND SELF-AWARENESS OF CONSTIPATION STATUSES AMONG YOUNG ADULTS FROM DIFFERENT FACULTIES AT ACIBADEM UNIVERSITY

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ABSTRACT

Aims: To evaluate Acıbadem University students' self-awareness of their constipation statuses and investigate whether there is an association between constipation and prolonged sitting time in the toilet affected by toilet habits. ***Methods:*** This cross-sectional study was conducted from March 7 to April 3, 2019, at Acıbadem Mehmet Ali Aydınlar University. The questionnaire consists of 3 parts and a total of 16 questions. The first part asked about the participants' gender, age, faculty, and school year to collect their demographic information. The second part investigated participants' awareness of constipation and factors affecting constipation. The last part included questions about toilet habits and their sitting time in the toilet. The constipation status of participants was evaluated using the Rome IV Diagnostic Criteria and the self-awareness of participants about their constipation statuses was assessed. ***Results:*** 293 students from 5 different faculties (Medicine, Pharmacy, Medical Engineering, Nutrition and Dietetics, and Psychology) of Acıbadem University participated in our study. Our results showed that 22.54% of students were appeared to be constipated. Out of all the students, 24.45% of them were unaware that they were constipated. The use of smartphones was the most common toilet habit, and it increased the time spent sitting on the toilet. Constipation was seen at higher rates among students who spent a longer time on the toilet. ***Conclusion:*** Our study demonstrated that having toilet habits increased the time spent sitting on the toilet. Our study also found that as the time spent on the toilet increased, the prevalence of constipation among participants increased accordingly. Poor eating habits and sedentary lifestyles of young adults may have a cumulative effect on constipation. Raising public awareness regarding proper defecation routines and limiting toilet habits and sitting time on the toilet seems essential to prevent constipation. ***Keywords:*** Constipation, toilets habits, lifestyle, smartphone, young adult

INTRODUCTION

Constipation can be defined as infrequent defecation or hard passage of stools (1). The prevalence of constipation is 8.3% in Turkey (2) and approximately 20% around the world (3-5), being one of the most common gastrointestinal complaints. However, it is still difficult to determine the exact prevalence of constipation since self-reported constipation is a subjective complaint dependent on the self-awareness and the definition used to identify "constipation". It has also been shown that self-reported constipation findings are neither sensitive nor specific compared to constipation diagnosis made with symptom-based criteria (5-7). The Rome IV Diagnostic Criteria are expert consensus criteria that have long been used by gastroenterologists for the diagnosis and classification of functional gastrointestinal disorders (8, 9). One of the criteria for the diagnosis of functional constipation is lumpy or hard stool defecation which is classified as Type 1 and Type 2 according to the Bristol Stool Form Scale is widely used in clinical practice for stool form measurement (10, 11). Additionally, many factors alter the prevalence of constipation such as age, gender, eating habits, water consumption, and physical activity (12-14). The prevalence of constipation increases in the elderly since the colonic transit time slows down with age. Moreover, women are 1.5 times more likely to be constipated than men (3). Insufficient fluid intake can also be one of the causative factors for constipation by forming a hard stool (15).

The study conducted by Dehn et al. (16) demonstrated the relationship between toilet habits and the risk of hemorrhoids. Goldstein et al. (17) attempted to examine the relationship between constipation and reading habits during defecation. However, this study included many bowel diseases besides constipation, and only toilet reading was questioned. In a recently published paper, Berney (18) stated that over the last few years they have been getting a lot of complaints from young adults with no significant risk factors referred to them with symptomatic hemorrhoidal disease. He found that the patients mostly reported prolonged sitting time on the toilet due to frequent smartphone usage therefore decided to ask patients presenting with gastrointestinal symptoms about their smartphone usage during their time on the toilet (18). In his paper, he named this situation the "Smartphone Lavatory Syndrome" (18). The study by Çelik (19) attempted to investigate the relationship between hemorrhoid incidence and smartphone use in Turkey, however, the study is not yet completed.

This study aims to evaluate Acıbadem University students' self-awareness of their constipation statuses and investigate whether

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there is an association between constipation and prolonged sitting time on the toilet induced by toilet habits.

MATERIAL AND METHODS

Research design

Our study was approved by the Acıbadem University Medical Research Ethics Committee (Protocol Code: ATADEK 2019-4/7). Informed consent was obtained from the students before they participated in the study. This study was conducted from March 7 to April 3, 2019, at Acıbadem Mehmet Ali Aydınlar University. The questionnaire in the Turkish language was carried out as handouts and distributed to participants via an interviewer. The questionnaire consists of 3 parts and a total of 16 questions (Table 1). The first part asked about the participants' gender, age, faculty, and grade to collect their demographic information. The second part investigated participants' awareness of constipation and factors affecting constipation (accommodation, water and fiber consumption, physical activity). The last part included questions about toilet habits (what they do on the toilet during defecation) and their sitting time on the toilet. Participants had to complete at least half of the questionnaire to be included in the study. The participants who completed less than half of the questionnaire were excluded from the study. Moreover, participants who completed more than half of the questionnaire but did not answer particular questions were excluded for only the questions that they did not answer. Additionally, participants were able to choose more than one option for the last question which asked about their toilet habits.

Table 1: The questionnaire used in the study.

Questions	*Answers*
1st Part: Demographics of Participants	
1) Gender	
2) Age	
3) Which faculty are you enrolled in?	
4) Which year are you enrolled in?	
2nd Part: Awareness of Constipation and Factors Affecting Constipation	
5) Which of the following do you think describes constipation?	a) Using the toilet less often b) Having difficulty in defecation c) Sitting on the toilet for a long time d) Bleeding while defecating e) Formation or palpation of hemorrhoids f) Lack of urge to defecate g) Bloating and excess gas in the intestines h) Other
6) Do you think you are constipated?	Yes / No / No idea
7) Please mark the criteria below that you have in at least 1 of every 4 stools (≥25%):	a) Straining during defecation b) According to the Bristol Stool Form Scale: Type 1 (separate, ball-like stools) or, Type 2 (lumpy, sausage-shaped stool) c) Sensation of incomplete evacuation after defecation d) Sensation of anorectal obstruction/blockage during defecation e) Use of drugs that facilitate defecation (laxatives) f) I do not experience any of the above
8) Choose the one that suits you from the following accommodation types:	With family / Dormitory or shared house / Other
9) Do you think you are eating a healthy and balanced diet?	Yes / No / No idea
10) How often do you consume fiber-rich foods such as fruits, vegetables, legumes, and cereals?	Every day / Few times a week / Once a week / Few times in a month / Once a month
11) How much water do you drink in a day approximately? (1 glass of water is about 200 mL)	<1 L / 1-2 L / 2-3 L / >3 L
12) When you think about your normal day, how active do you think you are?	I go on a walk every day / I go on a walk every other day / I go on a walk at least 3 days a week / I go on a walk once a week / I do not go on a walk routinely / Other (you can write down other sports you practice)
3rd Part: Toilet Habits and Sitting Time on the Toilet	
13) How often do you defecate?	More than once a day / Every day / More than 3 times a week / Less than 3 times a week
14) Do you have abdominal pain and/or abdominal bloating, discomfort that you feel relieved of when you go to the toilet?	Yes / No
15) Approximately how long do you stay on the toilet when you go to defecate? (in minutes)	<5 / 5-10 / 10-15 / 15-20 / >20
16) Are you being busy with something else while defecating?	a) Smoking b) Reading newspaper/ magazine c) Solving puzzle/sudoku d) Using cellphone/tablet e) Other f) None

The participants were able to choose more than one option for the 5th, 7th and 16th questions.

In the questionnaire, the Rome IV Diagnostic Criteria (Table 2) was used to diagnose whether participants are constipated or not (12). Furthermore, the Bristol Stool Form Scale (Figure 1) was added to the questionnaire to classify the participants' shape of stool (13). Besides, participants were asked to define constipation and indicate whether they think they are constipated or not to determine the participants' self-awareness of constipation. The 5th question aimed to determine the level of personal knowledge of constipation based on how well the participant knew the definition of constipation. If the participants who chose the correct definition of constipation here chose themselves as constipated in question 6 and were evaluated as constipated according to the Rome IV Diagnostic Criteria in question 7, this participant was considered to be "self-aware" of their constipation status, and the opposite situation was also valid. Therefore, the participant's self-awareness was a complex outcome that has emerged as a result of the analysis of the answers to more than one question. The participants' toilet habits were also investigated in the questionnaire. According to expert opinion, it is not recommended to sit on the toilet for more than 5 minutes. However, a span of 5 minutes may not be a very long time for the participants to notice that they have been sitting on the toilet for too long. Therefore, to ask if the participants had been sitting on the toilet for too long, the 10 minutes was deemed more appropriate to be included in the questionnaire.

Table 2: Rome IV Diagnostic Criteria for functional constipation.

Must include two or more of the following:
1. Lumpy or hard stools (Bristol Stool Form Scale 1-2) more than ¼ (25%) of defecations
2. Sensation of incomplete evacuation more than ¼ (25%) of defecations
3. Sensation of anorectal obstruction/blockage more than ¼ (25%) of defecations
4. Manual maneuvers to facilitate more than ¼ (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)
5. Fewer than three spontaneous bowel movement per week
6. Loose stools are rarely present without the use of laxatives
7. Insufficient criteria for irritable bowel syndrome
Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

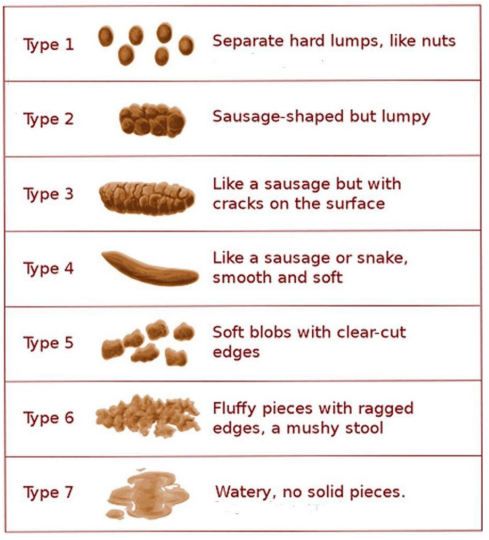

Figure 1: Bristol Stool Form Scale (11).
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Data analysis

The data were analyzed using Microsoft Excel (2016). The variables were tested for normal distribution by the Shapiro-Wilk Test. A p-value <0.05 was set for statistical significance. Numbers, percentages, mean, and standard deviation were used as the descriptive statistics for this study. Categorical variables were compared by using the Chi-squared test. The multivariate linear regression analysis was used to predict the value of constipation on the value of variables such as gender, age, accommodation, fiber consumption, water consumption, and physical activity.

RESULTS

This study was conducted on 293 students from the most populated 5 faculties of Acıbadem Mehmet Ali Aydınlar University. The results of this study were evaluated based on the answers of 291 students since 2 participants were excluded from the statistical analysis as they did not meet the inclusion criteria. A total of 80 medical students, 63 nutrition and dietetics students, 82 psychology students, 29 medical engineering students, and 39 pharmacy students were included in the study. The mean age of the students was 20.43 ± 1.73 years. Demographics of the participants are presented in Table 3.

Table 3: Demographics of participants.

	Number of Students [n (%)]
Gender	
Male	67 (23.0)
Female	223 (76.6)
Not specified	1 (0.3)
Age Group (years)	
18 – 20	169 (58.1)
21 – 23	117 (40.2)
> 23	5 (1.7)
Grade	
1	87 (29.8)
2	120 (41.2)
3	63 (21.6)
4	21 (7.2)
Faculty	
Medicine	80 (27.5)
Nutrition and Dietetics	62 (21.3)
Pharmacy	38 (13.1)
Medical Engineering	29 (9.9)
Psychology	82 (28.2)

According to the Rome IV Diagnostic Criteria, 64 (22.54%) participants were found constipated. Out of 291 participants, 45 (15.46%) of them described themselves as constipated. Out of 45 participants who described themselves as constipated, 34 (75.56%) of them were truly constipated according to the Rome IV Diagnostic Criteria. Moreover, 17 of 291 participants (5.84%) did not have an idea about their constipation statuses. The self-awareness of students on their constipation statuses is presented in Figure 2 and Figure 3. Medical students had the highest rate of awareness with 94.26% whereas nutrition and dietetics students were found to have the lowest awareness with 69%. Pharmacy, medical engineering, and psychology students' awareness rates were 85%, 82.96%, and 80.14%, respectively.

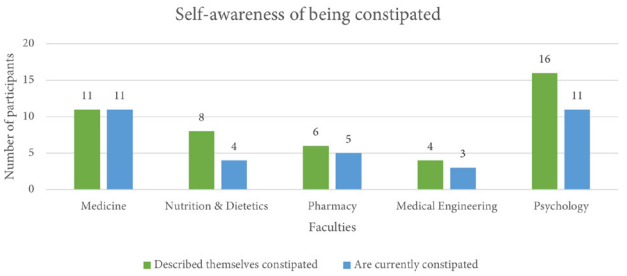

Figure 2: The comparison of students (Faculties of Medicine, Nutrition and Dietetics, Pharmacy, Medical Engineering, Psychology, respectively) according to their self-awareness on their constipation statuses (i.e. who was diagnosed as constipated and also defined themselves constipated as well).

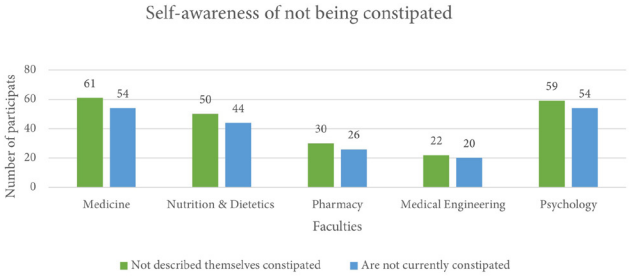

Figure 3: The comparison of students (Faculties of Medicine, Nutrition and Dietetics, Pharmacy, Medical Engineering, Psychology, respectively) according to their self-awareness on their constipation statuses (i.e. who was not diagnosed as constipated and also did not defined themselves constipated as well).

Table 4: Results of multivariate analysis with gender, age, accommodation type, fiber consumption, water consumption and physical activity as independent variables and constipation as the dependent variable.

Independent variables		*Beta coefficients*	*Standard Error*	*t Stat*	*P-value*
Intercept		*-0.077*	*0.100*	*-0.768*	*0.443*
Gender	*Female / Male*	*0.159*	*0.062*	*2.547*	***0.011***
Age	*>20 / =<20*	*-0.002*	*0.050*	*-0.041*	*0.967*
Accommodation type	*Dormitory / House*	*0.150*	*0.049*	*3.062*	***0.002***
Fiber consumption	*Everyday / Not everyday*	*0.023*	*0.052*	*0.436*	*0.663*
Water consumption	*=> 2L / Less than 2 L*	*-0.119*	*0.059*	*-2.038*	***0.042***
Physical activity	*At least 3 times a week / Less 3 times a week*	*-0.003*	*0.053*	*-0.051*	*0.960*

The multivariate linear regression analysis of different variables that could play a role in constipation is presented in Table 4. A significant regression equation was found (F(8.273) =4.066025, p<0.001) with an R2 of 0.11. According to participants' characteristics and preferences; gender, water consumption, and types of accommodation were significant predictors of the constipation status of participants (p=0.01, p=0.04, p=0.002, respectively). 28.24% of participants who were staying in a dormitory or a shared house were found to be constipated, while only 14.51% of participants who lived with their families were found to be constipated. Fiber consumption and physical activity were not significant factors for determining constipation status (p=0.66 and p=0.95, respectively). Smartphone/tablet use (69.76%) was the most common toilet habit among participants, whereas the rates of smoking, reading newspaper/magazines, and solving puzzles/sudoku were 5.5%, 4.12%, and 2.41%, respectively. 79 participants (27.15%) stated that they had no toilet habits. 81 of the participants who had at least one toilet habit, also had prolonged sitting time (>10 minutes) on the toilet. Table 5 shows that having toilet habits and prolonged sitting time on the toilet were significantly associated, (χ2(1, N=291) =12.569, p-value<0.001). Furthermore, 26 of the participants who were diagnosed as constipated according to Rome IV Diagnostic Criteria also had prolonged sitting time on the toilet. As shown in Table 6, being constipated and having a prolonged sitting time on the toilet had a significant association (χ2(1, N=284) =10.183, p-value =0.001). 60 participants who were diagnosed as constipated also had toilet habits. However, as shown in Table 7, there was no significant association between being constipated and having toilet habits (χ2(1, N=284) =3.293, p-value =0.07).

Table 6: The relationship between time spent on the toilet and state of constipation presented as numbers of participants (p-value =0.001).

	Diagnosed as constipated (n)	*Not diagnosed as constipated (n)*	*Total*
Sits on the toilet more than 10 minutes	26	46	72
Sits on the toilet less than 10 minutes	38	174	212
Total	64	220	***284***

(7 participants were excluded from the statistical analysis due to the incomplete filling of the questionnaire.)

Table 5: The relationship between participants' toilet habits and their time spent on the toilet presented as numbers of participants (p-value <0.001).

	Toilet Habits						
Time spent on the toilet	*Phone/tablet (n)*	*Newspaper/ magazine (n)*	*Puzzle (n)*	*Smoking (n)*	*Other (n)*	*None (n)*	*Total*
More than 10 minutes	63	6	4	5	3	10	91
Less than 10 minutes	141	6	3	11	2	69	232
Total	204	12	7	16	5	79	***323***

(Participants were allowed to choose more than one toilet habit.)

Table 7: Relationship of toilet habits and state of constipation presented as numbers of participants. Participants could choose more than one answer about their toilet habits if they have (p-value =0.07).

	Toilet Habits						
	Phone/Tablet (n)	***Newspaper/Magazine (n)***	***Puzzle (n)***	***Smoking (n)***	***Other (n)***	***None (n)***	***Total***
Diagnosed as constipated	50	2	3	5	0	12	72
Not diagnosed as constipated	149	9	3	10	3	65	239
Total	199	11	6	15	3	77	***311***

DISCUSSION

Although the use of smartphones and tablets on the toilet is very common, there are not many studies on the effects of using smartphones on the toilet on defecation disorders in the light of the literature. To our knowledge, this is the first study to present the frequency of toilet habits and the self-awareness of constipation statuses among young adults. Our study showed that having toilet habits was fairly common and was present in 72.85% of our participants. A study by Goldstein et al. (17) evaluated the prevalence of toilet reading habits in the Israeli adult population and found that toilet reading was prevalent in 52.7% of adults. In comparison, our study questioned several toilet habits such as the use of smartphones, solving puzzles, and smoking in addition to reading printed materials such as books, newspapers, and magazines. In contrast to the results of the aforementioned study, smartphone/tablet (69.76%) was found to be the most prominent habit in our study.

According to the literature, people with relatively unhealthy lifestyles and bad eating habits are more likely to experience constipation (13). However, our study did not show any significant association between constipation and fiber consumption or physical activity. On the other hand, types of accommodation and water consumption were significantly associated with constipation. Participants who stated that they live with families were found to be less constipated. This may be attributed to having more organized lifestyles and finely regulated circadian rhythm which controls gut motility (20, 21). Since less fluid consumption can increase the likelihood of constipation, the recommendation to increase fluid intake for patients with constipation will be appropriate. Consequently, the type of accommodation and water consumption are significantly related to constipation. Therefore, to prevent and treat constipation in young adults, it is important for them to consume sufficient water and accommodate in a regular place that supports their circadian rhythms.

Another key finding in our study was that participants who had at least one toilet habit were found to be more constipated. 25.7% of participants who had toilet habits were constipated while only 15.5% of participants who did not have any toilet habits were constipated. However, our study did not find any significant association between toilet habits and constipation. It seems that extensive smartphone use during defecation (69.76%) is not a distinctive factor in our study population due to its popularity among both constipated and non-constipated participants. Since young adults lead smartphone use in the general population, further studies may be conducted in a broader age group to provide more accurate results (22). Since the rate of smartphone use is lower in other age groups, this could act as a distinctive factor (22).

Our study showed that having toilet habits was significantly associated with prolonged sitting time (>10 minutes) on the toilet. Having constipation and prolonged sitting time on the toilet was also found to be significantly associated. Such a result can be attributed to the expulsion of hard and lumpy stools, which requires more time since it takes more force and coercion to expel the hard stools. However, prolonged sitting on the toilet can lead to hemorrhoids and exacerbate constipation (16). Based on these findings, it seems necessary to raise public awareness by training on reducing the prevalence of anorectal disorders and limiting toilet habits and the time spent on the toilet. Medical students were the group with the highest awareness of constipation in our study, possibly more familiar with the symptoms that contribute to constipation, given their medical education. Similarly, if constipation becomes more recognized by the public, adjusting some routines on their own, such as increasing water intake, limiting toilet habits, and time spent on the toilet, will help alleviate patients' symptoms and complaints.

Our study provided an integrated approach to constipation that includes many independent variables. However, several potential limitations arose due to the demographics of our population. The fact that women were in the majority at the Acıbadem University at the time of the survey may have created a gender imbalance. Further studies may involve a wider age group and a more balanced gender distribution.

In conclusion, having toilet habits is a common trait that may increase the time spent sitting on the toilet, which can lead to issues in the anorectal system. Moreover, young adults with toilet habits tend to be more constipated, although a significant association has yet to be shown. Constipation status and time spent on the toilet were found to be significantly associated. Water intake and type of accommodation were found to be significantly associated with constipation. Raising public awareness regarding proper defecation routines and limiting toilet habits and sitting time on the toilet seems essential to prevent constipation.

Ethics Committee Approval: This study was approved by the Acıbadem University Medical Research Ethics Committee (Protocol Code: ATADEK 2019-4/7).

Informed Consent: Written informed consent was obtained from the participants of this study.

Conflict of Interests: The authors declared no conflict of interest.

Author contributions: Concept: NK, AD, HK, CHD. Design: NK, AD, HK, CHD. Supervision: OE. Resources: NK, AD, HK, CHD. Materials: NK, AD, HK, CHD. Data Collection and/or Processing: NK, AD, HK, CHD. Analysis and/or Interpretation: NK, AD, HK, CHD. Literature Search: NK, AD, HK, CHD. Writing Manuscript: NK, AD, HK, CHD. Critical Review: NK, AD, HK, CHD, OE.

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RETROSPECTIVE ANALYSIS OF FOLLICULAR LYMPHOMA PATIENTS IN TRAKYA UNIVERSITY SCHOOL OF MEDICINE: A SINGLE CENTER EXPERIENCE

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ABSTRACT

Aims: To establish a dataset including demographic features, disease characteristics, and survival rate of follicular lymphoma patients in Trakya University School of Medicine and contribute to the database of follicular lymphoma in Turkey. ***Methods:*** In this retrospective cross-sectional study, we analyzed data constituting of follicular lymphoma patients over 18 years of age followed during the years of 2015-2020 in Trakya University Division of Hematology. ***Results:*** Out of 43 patients, 22 (51.2%) were female and 21 (48.8%) were male. The mean age was 56.56 (standard deviation 13.24) years. There were 5 (11.6%) patients with B symptoms, presence of bone marrow involvement was seen in 17 (39.5%) patients, lastly, there were 18 (41.9%) patients with splenomegaly. Twenty-one (48.8%) patients received rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone, making it the most common treatment protocol administered in our study. ***Conclusion:*** Follicular lymphoma patients usually end up getting diagnosed at an advanced stage of the disease, presenting with incidentally noticed painless lymphadenopathy. Additionally, based on evidence in the literature, a clear gap in the successful diagnosis of follicular lymphoma patients can be observed between developed and developing countries. To overcome this hurdle, enhanced cooperation with hematopathology may lead to an increased awareness enabling physicians to make a more accurate diagnosis. Nonetheless, further studies are still needed to fully apprehend the epidemiology of follicular lymphoma patients in Turkey. ***Keywords:*** Follicular lymphoma, retrospective study, non-Hodgkin's lymphomas

INTRODUCTION

Representing more than 20% of all non-Hodgkin's lymphomas (NHLs), follicular lymphoma (FL) is the most common indolent systemic lymphoid neoplasm originating from germinal core B cells, both centrocytes, and centroblasts, usually exhibiting a follicular growth pattern (1-3). Having a higher incidence (7/100.000) in western countries, it primarily occurs in adults, mean age of 65, with a male-to-female ratio of 1: 1.7 (4). An increased risk factor in the growth of tumor has been linked in patients who had higher exposure to herbicides and pesticides (5).

Most FL patients exhibit a widespread disease at diagnosis, characterized by generalized painless lymphadenopathy, splenomegaly, and bone marrow involvement, whereas extranodal involvement is less common. B symptoms (weight loss, fever, and night sweats) are usually seen in 20% of the patients (6). Change in clinical course, rapid enlargement of a mass, B symptoms, and abnormal laboratory findings (elevated serum lactate dehydrogenase (LDH)) could indicate transformation to a more aggressive type of non-Hodgkin's lymphoma (NHL), for example, diffuse large B cell lymphoma (a phenomenon also known as Richter's syndrome) (2, 6).

The patient's evaluation should be made through his history, laboratory findings, physical examination, and imaging. Diagnosis is made with histopathological findings of an excisional lymph node biopsy. More than 85% of cases have a characteristic (14:18) translocation – a fusion between the BCL-2 gene on chromosome 18 and the IgH locus on chromosome 14 (7).

Histopathologically, World Health Organization (WHO) classifies FL into 3 grades according to the number of centroblasts (large unnotched follicle cells) spotted per high-power field (2). As for disease staging, the Ann Arbor system plays a crucial role together with modified Groupe d'Etude des Lymphomes Folliculaires (GELF) or British National Lymphoma Investigation criteria in determining the choice of treatment (8). Furthermore, prognostic tools established before the rituximab era, so-called FL International Prognostic Index (FLIPI) and FLIPI-2, are frequently used for risk assessment (8). Development into a more aggressive phenotype is observed at 5 years in 11-13%, and at 10 years in 15-28% of the patients (1, 6).

Disease management strategies include a watch-and-wait approach, immunochemotherapy, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), single-agent therapy, and radiotherapy (3, 9). In terms of progression-free survival, favorable outcomes are noted in watch-and-wait and single-agent therapy options. Bone marrow transplantation is the preferred management in patients with a relapsed/refractory clinical course or Richter's syndrome. Thus, a better understanding of the tumor's genetic map and microenvironment may provide hope for novel targeted therapies in FL patients.

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This retrospective study aims to establish data; including demographic features, disease characteristics, and total follow-up of FL patients in Trakya University School of Medicine and contribute to the database of FL patients in Turkey.

MATERIAL AND METHODS

This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2020/339). Analyzed data constituted FL patients over 18 years of age followed during the years of 2015-2020 in Hematology Division, Trakya University School of Medicine. Patients' data compromised their age, gender, date of diagnosis, last inspection date, neutrophil count, LDH levels, Ann Arbor scores, lymph node involvement, bone marrow involvement, serum β2 microglobulin levels, the existence of B symptoms, and treatment method initiated.

Numbers, percentages, mean and standard deviation (SD) were used as the descriptive statistics. The variables were tested for normal distribution by the Shapiro-Wilk test. Normal distribution was observed in age, lymph node involvement number, neutrophil count, and platelet count, thus they were presented as mean ± SD. Non-normal distribution was observed in gender, duration of total follow-up, hemoglobin levels, serum β2 microglobulin, and LDH levels, which were presented as median and inter-quartile range (IQR). WHO classification, Ann Arbor stage, FLIPI-1, and FLIPI-2 scores, GELF criteria, B symptoms, bone marrow involvement, splenomegaly and treatments were presented as numbers and percentages. Kaplan-Meier analysis was used to demonstrate patients' total follow-up. A p-value <0.05 was set for statistical significance. The data were analyzed with IBM SPSS version 23.0.

RESULTS

Out of 43 FL patients, 22 (51.2%) of them were female and 21 (48.8%) of them were male. The mean (SD) age was 56.56 (13.24) years. There were 5 (11.6%) patients with B symptoms, presence of bone marrow (BM) involvement was seen in 17 (39.5%) patients, and lastly, there were 18 (41.9%) patients with splenomegaly. The summary statistics for the demographic data and total follow-up of FLIPI scores of patients are presented in Table 1 and Figure 1.

According to the WHO classification for FL, there were 9 (20.9%) grade 1, 17 (39.5%) grade 2, 3 (7.0%) grade 3, 6 (14.0%) grade 3A, 1 (2.3%) grade 3AB, and 5 (11.6%) grade 3B patients, and 2 (4.7%) with missing data. According to the Ann Arbor staging system, there were 5 (11.6%) patients in stages I-II, 31 (72.1%) patients in III-IV, and 7 (16.3%) missing data. Based on GELF criteria, there were 16 (37.2%) patients with 0 points, 8 (18.6%) patients with 1 point, 11 (25.6%) patients with 2 points, 7 (16.3%) patients with 3 points, and 1 (2.3%) patient with 4 points.

Summary statistics for numerical data of treatment methods applied to patients are presented in Table 2. There were 3 (7.0%) patients with Richter's syndrome, and 2 (4.7%) patients with skin involvement. The mean ± SD for number of lymp nodes involved was 7.43 ± 5.28, for the neutrophil count was 4384 ± 1858 mm3, and for the platelet count was 230.74 ± 93.44 mm3. Median (IQR) for hemoglobin was 13.30 (3) g/dL, for lactate dehydrogenase was 210.00 (182) U/L, and for serum β2-microglobulin was 2408 (2796) mcg/mL.

Table 1: Summary statistics for demographic data, total follow-up of FLIPI scores of patients.

	Number of patients (n= 43)
Gender [n (%)]	
Female	22 (51.2)
Male	21 (48.8)
Age of the patients during diagnosis (years)	56.53 ± 13.24
Total follow-up (months)	36 (43)
FLIPI-1 score [n (%)]	
Low-Risk (0-1)	13 (30.2)
Intermediate-Risk (2)	16 (37.2)
High-Risk (≥3)	14 (32.6)
FLIPI-2 score [n (%)]	
Low-Risk (0-1)	22 (51.2)
Intermediate-Risk (2)	7 (16.3)
High-Risk (≥3)	14 (32.6)

FLIPI: *Follicular Lymphoma International Prognostic Index*

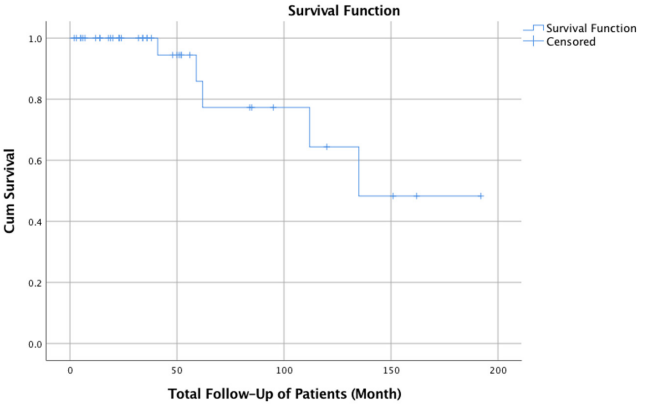

Figure 1: Kaplan-Meier survival analysis of patients' total follow-up.

Table 2: Summary statistics for treatment protocols administered.

Treatment Protocol	*1st Line Treatment N(%)*	*≥ 2nd Line Treatment N(%)*
Watch and Wait	1 (20.9)	
R-CHOP	23 (53.5)	
R-CVP	9 (20.9)	1 (2.3)
R-ICE		2 (4.7)
R-BENDA	3 (7.0)	
R	9 (20.9)	1 (2.3)
R-CEOP	1 (2.3)	
Obinutuzumab, Lenalidomide and Bendamustine		1 (2.3)
Radiotherapy	1 (2.3)	1 (2.3)

N: *Number,* ***R-CHOP:*** *Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone,* ***R-CVP:*** *Rituximab, cyclophosphamide, vincristine sulfate, and prednisone,* ***R-ICE:*** *Rituximab, ifosfamide, carboplatin, and etoposide phosphate,* ***R-BENDA:*** *rituximab and bendamustine,* ***R:*** *Rituximab,* ***R-CEOP:*** *Rituximab, cyclophosphamide, etoposide, vincristine, prednisone*

DISCUSSION

The primary objective of this retrospective study was to analyze FL patients' demographic features, disease characteristics, overall survival and treatment methods followed during the years of 2015-2020 in the Hematology Division of Trakya University School of Medicine.

The mean age in our study was 56.56 years, slightly lower compared to the results of Becnel et al. (10), which was between 60-70 years of age. However, results in the study conducted by Federico et al. (11) were in line with ours, regarding age and gender demographics. In our study, 51.2% of the patients were female and 48.8% were male, whereas their patient percentages were 53% female and 47% male. The difference between the two studies was the patient population, Federico et al. (11) studied 987 patients, whereas 43 patients were studied in ours. A similar database to ours, Kahraman et al. (12) had 17 female (60.7%) and 11 male (39.3%) patients, however, 50% (12) of their patients were younger than 60 years, and the other half were older.

Observing the overall number of lymphoma patients followed in our hospital between the years of 2015-2020, there were 87 Hodgkin's lymphoma and 566 NHL patients, of which 43 (7.6%) were FL patients (unpublished data, personal communication with Kirkizlar et al.). Our results were collateral with a similar study carried out in Turkey by Kahraman et al. (12) suggesting that FL can be seen in 9% of all NHLs in Turkey. On the other hand, Carbone et al. (13) reported that FL may represent up to 20-25% of NHL in developed countries, based on evidence reviewed, a clear gap between patients in developed and developing countries is discernible when it comes to diagnosis of FL. This gap is may be attributed to the lack of resources physicians have in order to produce accurate diagnoses. In such cases, enhanced cooperation with hematopathology could lead to increased awareness, feasibly to a more accurate diagnoses (14).

In B cell lymphomas, involvement of the spleen is usually evident but marked splenomegaly as a main finding in FL is rare (4). Despite that, 41.9% of patients had splenomegaly, which is much higher than the results of Koiso et al. (14). Although BM involvement may be present in up to 50-60% of patients, it was seen in 40.5% of the patients in our study. Finally, in terms of B symptoms, our results were parallel with Federico et al. (11), 15% of their patients exhibited B symptoms whereas 13.5% exhibited it in ours.

Both for Hodgkin's and non-Hodgkin's lymphomas, the Ann Arbor staging system is used for staging the disease. The designations for the four different stages (I-IV) are A, B, E, and S, which reflect the patient's symptomatic findings. In our study, 5 (11.6%) patients were in stages I-II and 31 (72.1%) patients were in stages III-IV. Likewise, Federico et al. (11) had 250 (25%) patients in stages I-II and 737 (75%) of their patients were in stages III-IV.

In 2004, the FLIPI was assembled as a prognostic tool to facilitate estimating patients' overall survival based on their clinical information (15). Five different parameters are used; age (>60 vs <60 years), Ann Arbor stages (III-IV vs I-II), anemia (hemoglobin <120 vs ≥120 g/L), number of LN area involved (>4 vs ≤ 4), and serum LDH levels (elevated vs normal) (15). A point is granted when the answer is the first one out of the two choices cited above. Classification is made based on points acquired, 1 point is the low-risk group, which equals 70%, 2 points is the intermediate-risk group, which equals 50%, and 3 or more points means high risk, which equals 35% of the patients that had 10-years of overall survival. In comparison with 51 months in Frederico et al. (11) study, findings regarding total follow-up of patients after their initial diagnosis were around 50 months in our study.

Standard initial treatment for symptomatic advanced indolent NHL is a rituximab-based immunochemotherapy regimen. Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy has shown prominent results in progression-free survival, in addition, rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP) regimen demonstrated an improvement in overall survival of patients (16, 17). Yet, results in BRIGHT study elucidated how bendamustine and rituximab combination was non-inferior to standard treatment regimen (18). A study previously discussed, conducted in Turkey by Kahraman et al. (12), used four different methods as first-line treatment: watch and wait, radiotherapy, chemotherapy, and rituximab. Percentages of their administrations were sequentially 7.1%, 14.3%, 78.6%, and 40%. Demonstrating similar results, our study also had watch and wait (18.6%), chemotherapy: R-CHOP, R-CVP (81.4%), rituximab (20.9%), and radiotherapy (2.3%). Moreover, Obinutuzumab, lenalidomide, and bendamustine combination and rituximab with ifosfamide, carboplatin, and etoposide phosphate were used for the second-line treatment in our study.

In this retrospective study, the patient population was one of our main limitations while comparing our results with current literature. Our study also lacked some of the patients' information regarding their total follow-up, Ann Arbor stages, B symptoms, BM involvements, LN involvements, and treatment method due to missing data in patients' files.

In conclusion, despite being the most common NHL, FL usually ends up getting diagnosed at an advanced stage of the disease, presenting with incidentally noticed painless lymphadenopathy following a painless clinical course. This study aimed to make a contribution to current literature on the subject of demographic features, disease characteristics, total-follow up, and treatment methods. Furthermore, based on the evidence we have reviewed, a clear gap between patients in developed and developing countries can be observed in the diagnosis of FL. To overcome this hurdle, enhanced cooperation with hematopathology could lead to increased awareness, enabling physicians to make a more accurate diagnosis. Thus, further studies are required to fully apprehend the epidemiology of FL patients in Turkey.

Ethics Committee Approval: This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TUTF-BAEK2020/339).
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CASE REPORT OF AN INCIDENTAL UNICENTRIC CASTLEMAN DISEASE

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ABSTRACT

Aims: To emphasize the hardship of diagnosing Castleman disease and present a potential treatment method. ***Case Report:*** A sixty-three-year-old male patient was admitted to the outpatient clinic with an attack of acute cholecystitis. The patient's abdominal computed tomography revealed an incidentally detected lipid dense solid mass (64x53x37 mm) at the level of right renal hilum with 29x13 mm solid components in the middle. The patient was admitted to the urology department and underwent surgery where the mass was totally excised due to suspicion of a malignancy (liposarcoma). Histopathological examination later on resulted with unicentric Castleman disease, hyaline vascular subtype. ***Conclusion:*** Since unicentric Castleman disease has an asymptomatic clinical course and is quite rare, it is necessary to rule out many potential possibilities before reaching a proper diagnosis. However, unicentric Castleman disease usually exhibits a good prognosis after the removal of the affected lymph node. Still, Castleman disease should be a candidate considered in the differential diagnosis of patients with incidentally discovered lymphadenopathy. On the whole, for a better understanding of underlying pathophysiology, there still lies a gap to be filled with knowledge acquired through further studies. ***Keywords:*** Castleman disease, lymphoproliferative disorder, lymphadenopathy

INTRODUCTION

First described by Benjamin Castleman in 1954 as a rare lymphoproliferative disorder, Castleman disease (CD) can be separated into two main groups based on the number of lymph nodes involved: unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) (1). While UCD affects only a single lymph node or lymph node chain, MCD is a more widespread disease (2). Lymph nodes of the trunk, neck, and abdomen are affected by 70, 15, and 15%, respectively. Additionally, there have been cases reported with affected lung, larynx, parotid, pancreas, and meninges (3). A study aiming to elucidate the incidence rate of CD found the rate to be 21-25 per million persons per year, with UCD being the most common type (4). Thus, the etiology of the disease has not been fully understood due to its rarity and clinical heterogeneity. The five-year overall survival rate is 91% in UCD (5). Diagnosis is made with the biopsy of the affected lymph node (5).

Histological classification of CD is characterized with 3 variants: hyaline vascular (HV), the plasma-cell, and the mixed form variant (2). Unicentric presentation most commonly demonstrates HV, whereas MCD presents plasma-cell or mixed variant more (6). CD is usually associated with increased production of interleukin-6 (IL-6), where the plasma-cell variant has been linked with human immunodeficiency virus (HIV) and human herpesvirus 8 (HHV-8) (1, 2). Although different therapeutic approaches are defined for the diagnosis and treatment of UCD, excision is still the gold standard (7).

By presenting this rare case of UCD we aim to raise an awareness of CD's inclusion as an entity in differential diagnosis with patients who have single or more lymphadenopathy and put forward a potential treatment method.

CASE REPORT

A sixty-three-year-old male patient was admitted to the outpatient clinic of Trakya University Hospital with an attack of acute cholecystitis. In the patient's past medical history, he had a diagnosis of hypertension. In the outpatient clinic examination, the patient's onset blood pressure, heart rate, and body temperature were normal, whereas he had gastrointestinal symptoms and weight loss. His physical examination revealed there was no bilateral costovertebral angle sensitivity. The routine hemogram, urinalysis, and serum electrolytes were normal. Ultrasonography was performed in the emergency department and no stones were found in the gallbladder. After the USG, a computed tomography (CT) scan was performed as well. In the patient's abdominal CT scan an incidental lipid dense mass of 64x53x37 mm was detected at the right renal hilum level with 29x13 mm solid components in the center (Figure 1).

Liposarcoma had been considered in the differential diagnosis and the total excision of the mass had been planned for the exact diagnosis and treatment. The patient was operated on and followed by the urology department. The operation was performed with an anterior subcostal incision. After the colon was medialized, the re-

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nal vein and artery were reached while protecting the duodenum. Mass was later on excised due to a suspicion of malignancy. Postoperative follow-up was uneventful and hematological blood tests were found to be normal.

Liposarcoma and primary renal cell carcinoma (hypercalcemia, fever, and erythrocytosis were not present) were considered in the differential diagnosis. Total excision of the mass has been planned both for the exact diagnosis and treatment. The patient was admitted to the hospital and later was operated on by the urology department. The operation was performed with an anterior subcostal incision. After the colon was medialized, the renal vein and artery were reached while protecting the duodenum. The mass was excised due to a malignancy suspicion. The cholecystectomy was also performed during the operation. The postoperative follow-ups were done by the hematology department. The follow-up was uneventful and hematological blood tests were found to be normal.

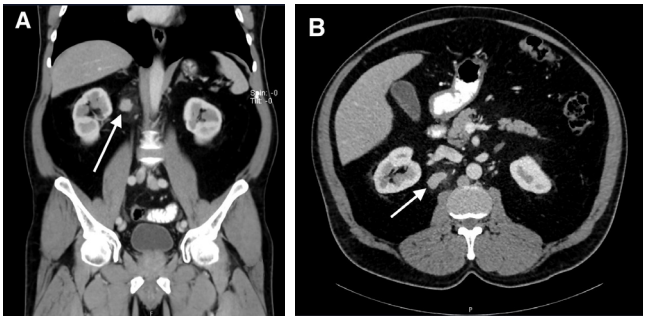

Figure 1: A: Coronal plane of abdominal CT scan (lipid dense mass shown with the arrow). B: Transverse plane of abdominal CT scan (lipid dense mass shown with the arrow).

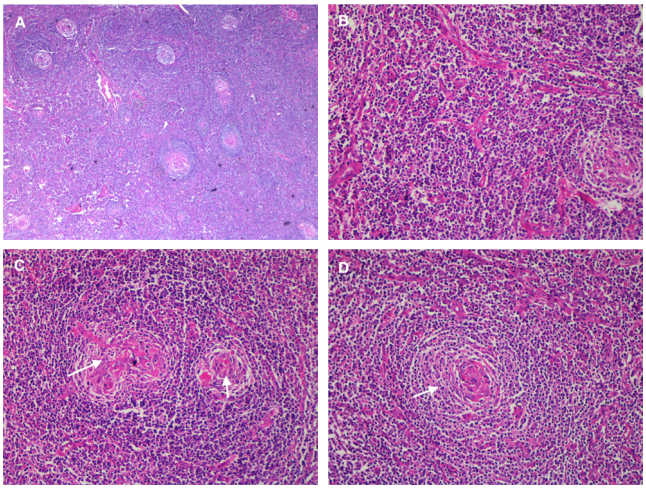

Figure 2: A: Involuted lymphoid follicles distributed in lymph node parenchyma and vascularized structures with hyalinized walls aligned with hyperplastic endothelium in the interfollicular zone (H&E, x100). B: Incrementation of hyalinized vascular structures created by hyperplastic endothelium in interfollicular spaces and regressing lymphoid follicle on the right (H&E, x400). C: The view of Castleman disease's characteristic structure "Lollipop follicle" shown with the white arrows, atrophic germinal center, and hyalinized small vein of lymphoid follicle (H&E, x400). D: The typical "onion skin pattern" view (Arrow), which is common to be seen in hyalinized germinal center together with concentrated layers of small uniformed Mantle zone lymphocytes (H&E, x400).

Following patient's surgery, the specimen was sent to the pathology department for further analysis. Histopathological examination resulted with CD, hyaline vascular subtype. The HHV-8 test, which was performed to determine the type of CD, was negative. In addition, B lymphocyte markers were checked in order to exclude lymphoma. The immunohistochemical analysis results were as follows: mantle zone lymphocytes were stained with the IgM, OCT-2 and PAX5 stained the atrophic follicules, MUM1 stained the plasma cells and the BCL-6 test was positive at the atrophic germinal centers. Characteristic HV histological patterns such as involuted lymphoid follicles, incrementation of hyalinized vascular structures, lollipop follicle and onion skin pattern on the hyalinized germinal center were found (Figure 2). In addition, positive staining for CD20 in germinal center (Figure 3A), positive staining for CD21 antibody of dendritic cell population in germinal centers (Figure 3B) and positive staining for CD 3 antibody in T lymphocytes around germinal centers (Figure 3C) were seen.

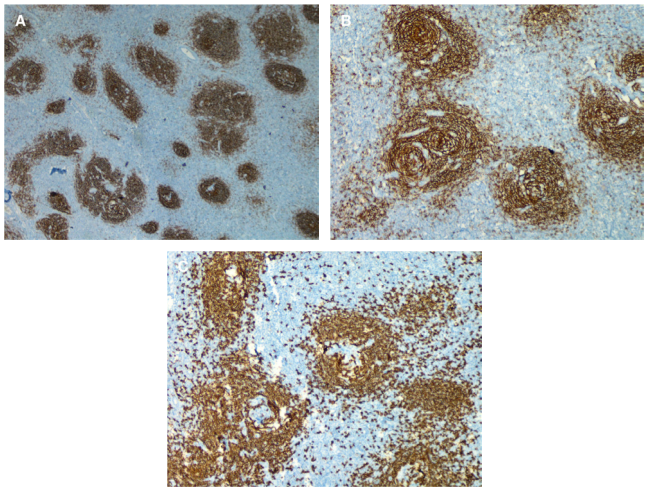

Figure 3: Immunohistochemical analysis. A: Positive staining for CD20 antibody in germinal center of different sizes (magnification x100). B: Positive staining for CD21 antibody of dendritic cell population in germinal centers with locally clinging patterns (magnification x200). C: Positive staining for CD 3 antibody in T lymphocytes around germinal centers (magnification x200).

DISCUSSION

Since UCD is often asymptomatic, early diagnosis may not always be possible. In some cases, especially the ones with retroperitoneal masses, tumors may have different appearances, which makes the pre-operative diagnosis exceedingly difficult (8). An enlarged lymph node can be detected incidentally during a physical examination or imaging test performed for another reason. Nakata et al. (9) presented a 47-year-old with a mass in pelvic retroperitoneum, incidentally diagnosed case with no systemic symptoms such as pelvic pain, fatigue, fever, or weight loss. In addition, the patient's serum levels of carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, CA125, and interleukin 6 (IL-6) were within the normal range. While the mass is usually detected incidentally, as Nakata et al. (9) reported, it can also manifest itself with specific symptoms caused by the effect of the mass or adjacent organs (10, 11). There have been individuals reported with palpable masses and dyspeptic symptoms (10, 11). Hence, these studies indicate how complicated the diagnosis of CD can be.

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In our case, a lipid dense solid was incidentally detected at the level of the right renal artery on CT, performed during an attack of cholecystitis. Patients with acute cholecystitis usually present with symptoms of unremitting right upper quadrant pain, anorexia, nausea, vomiting, and fever as in our case (12). Gallbladder wall thickening, pericholecystic fluid, or a sonographic Murphy's sign are among the typical diagnostic findings (13).

The clinical presentation of CD is usually associated with autoimmune and infectious diseases. Excessive production of IL-6 and a viral analog of IL-6 are important factors of pathogenesis (2). Moreover, the plasma-cell variant is associated with HIV and human herpesvirus 8 (HHV-8) infections (1). Our case was HHV-8 negative, thus plasma-cell variant possibility was excluded.

There are mainly two subtypes of UCD hyaline vascular variant and the plasma-cell variant. The HV variant's histological pattern is usually diagnostic with multiple tight aggregates of follicular dendritic cells or atrophic follicles (1). On the other hand, the plasma cell variants of CD are less-defined histologically (1). Our patient's CD was an HV variant, thus some characteristic histological patterns such as involuted lymphoid follicles (Figure 2A), incrementation of hyalinized vascular structures (Figure 2B), hyalinized arteriole characterized with lollipop follicle (Figure 2C) and onion skin pattern on the hyalinized germinal center (Figure 2D) were seen clearly.

Treatment response is evaluated by normalization of previous clinical/laboratory norms after lymph nodes are completely removed (7). Corticosteroids and rituximab or adjuvant radiotherapy are the preferred options in reducing tumors too large for removal (14). Although radiotherapy can be applied to patients who cannot be operated due to comorbidities or residual tumor remains, surgical excision of the mass should still remain as the primary treatment option (14). For this reason, the medical team should carefully scrutinize all aspects and risk factors before reaching a consensus for the treatment.

In conclusion, various other possibilities are ruled out first on the path of diagnosing CD. The reason being that it is asymptomatic in most cases and is extremely rare. Despite that, UCD patients usually exhibit a good prognosis after the affected lymph node is excised. Therefore, surgical excision still remains an important and effective treatment option. Nonetheless, we hope that this case report will give physicians a better insight into this rare event.

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INCIDENTAL DETECTION OF PREVIOUSLY UNKNOWN BREAST CANCER ON Tc-99m MIBI SCINTIGRAPHY

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ABSTRACT

Aims: Tc-99m methoxyisobutylisonitrile scintigraphy is a diagnostic method commonly used for cardiac perfusion imaging. It is also used for parathyroid, lung, breast, thyroid, brain, melanoma, lymphoma, bone, and soft tissue primary and secondary tumors imaging. Our case aims to report a breast cancer incidentally revealed by Tc-99m methoxyisobutylisonitrile scintigraphy. ***Case Report:*** A 49-year-old female patient was admitted to the cardiology department with atypical angina. Tc-99m methoxyisobutylisonitrile scintigraphy showed myocardial perfusion was within normal limits but a focal uptake was detected in the lateral superior quadrant of the left breast. Ultrasonography detected a lesion with irregular borders in the outer quadrant of the left breast and a lymph node with increased thickness of the cortex in the left axilla. Magnetic resonance imaging showed a mass with a spiculated contour in the outer quadrant of the left breast and lymph nodes with increased cortex thickness in both axillae. By the histopathologic examination, the specimen was diagnosed with invasive ductal carcinoma. ***Conclusion:*** Although Tc-99m methoxyisobutylisonitrile scintigraphy is mainly used for myocardial perfusion imaging, the entire image area should be examined in detail and further investigation should be done for incidental focal lesions that were previously undetected.
Keywords: Tc-99m methoxyisobutylisonitrile, breast cancer, scintigraphy, incidental

INTRODUCTION

Tc-99m methoxyisobutylisonitrile (MIBI) is a lipophilic, monovalent cationic isonitrile compound. It passively diffuses across the cell membrane and is sequestered in the mitochondria (1). Tc-99m MIBI scintigraphy is currently a commonly used diagnostic method for cardiac perfusion imaging (2). Myocardial perfusion scintigraphy is a noninvasive modality widely used in the evaluation of myocardial ischemia. Perfusion defects have been linked to areas supplied by significantly stenosed coronary arteries (3). It is also used for parathyroid imaging, especially for parathyroid adenomas and lung, breast, thyroid, brain, melanoma, lymphoma, bone, and soft tissue primary and secondary tumors imaging (4). With this case report, we aimed to report a breast cancer that was found incidentally by Tc-99m MIBI scintigraphy.

CASE REPORT

A 49-year-old female patient with rheumatic mitral valve disease and scoliosis was admitted to the cardiology department with atypical angina. After clinical examination, Tc-99m MIBI scintigraphy was requested for ischemia detection.

Myocardial perfusion was within normal limits in the MIBI images and ischemia was ruled out, however, a focal uptake was detected in the lateral superior quadrant of the left breast (Figure 1 A-B). Therefore, the patient was referred to the general surgery department for further examination. After clinical examination, breast ultrasonography (USG) and breast magnetic resonance imaging (MRI) were requested. USG revealed a 17x8 mm lymph node with increased cortex thickness in the left axillae.

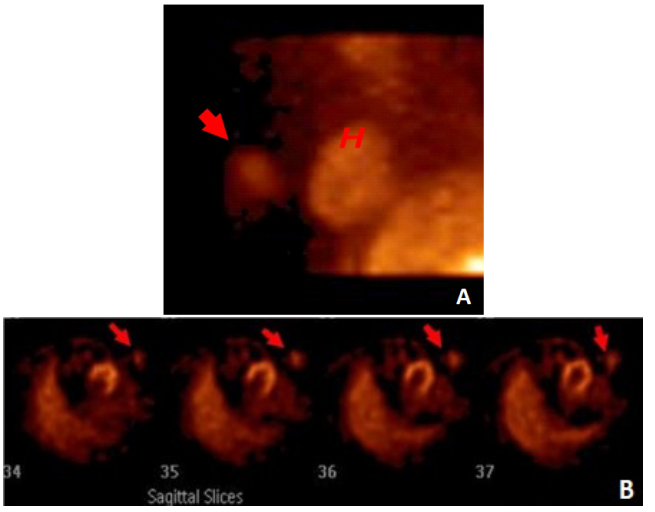

Figure 1: A: Tc-99m MIBI scintigraphy raw image indicating focal uptake in the lateral superior quadrant of the left breast (H: heart) (Arrow). B: Tc-99m MIBI scintigraphy sagittal sectional images with focal uptake in the left breast (Arrows).

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In the outer quadrant of the left breast, a lesion with 35x22 mm in size and irregular borders was observed. This lesion also created retraction in surrounding tissues. A few more satellite nodules were observed in the neighborhood of the lesion. The MRI scan detected an irregularly shaped lesion in the outer quadrant of the left breast, 36x12 mm in size, with a contoured spicule that has been followed (Figure 2). The mass was found to be extended along the lesion ductus. The left breast skin seemed diffusely thickened. An approximately 10x3 mm asymmetric contrast enhancement area is observed in the outer quadrant of the right breast areola plane. In both axillae, lymph nodes with increased cortex thickness were also seen.

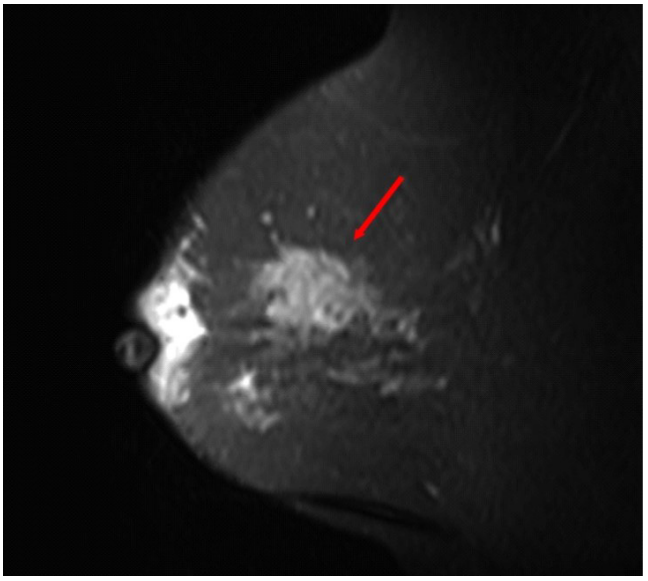

Figure 2: Irregularly shaped lesion (red arrow) in the outer quadrant of the left breast on MRI.

Histopathological evaluation of the surgical specimen confirmed the incidental diagnosis of breast cancer. The histopathologic examination result of the specimen was invasive ductal carcinoma. The tumor was staged as pT1N1M0.

DISCUSSION

Tc-99m MIBI is especially used for myocardial perfusion imaging. However, incidental uptake on the areas of rotating raw SPECT images have also been detected (2). These findings may alert physicians to a condition that needs to be further examined, such as breast cancer.

In tumor cells, MIBI retention is dependent to cellular and mitochondrial membrane potential and ATP-powered efflux pump such as P-glycoprotein (5). The initial use of Tc-99m MIBI for breast cancer was reported by Aktolun et al. (6) in 1992. Afterwards, it has been evaluated by many other researchers for the imaging of breast cancer lesions and the prognostic value for chemotherapy response (2). It was found to make unique contributions in select patients such as women with dense breasts or nonpalpable mammographically indeterminate lesions or palpable abnormalities (7). Although scintimammography is not used as the primary diagnostic method, it can be used in select cases where other diagnostic methods are indeterminate. It is also recommended for sentinel lymph node detection in breast cancer (8, 9). The sensitivity and specificity of Tc-99m MIBI scintigraphy are 75.4% and 82.7%, respectively (7). Therefore, it is important to evaluate the chest wall, even if the examination was performed for other purposes such as for myocardial perfusion, as seen in this case.

In imaging studies, incidental lesions are not uncommon. There are cases reported in the literature in which breast cancer was incidentally detected during imaging with Tc-99m MIBI for the diagnosis of other pathologies (10, 11). As in this case, patients may have breast lesions or other masses that are not yet known by their clinicians.

In conclusion, even though Tc-99m MIBI scintigraphy is mainly used for myocardial perfusion imaging, the entire image field should be evaluated meticulously, and any incidental focal lesions should be further examined in case of a previously undetected condition.

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MANAGEMENT OF A T-TUBE MIGRATION INTO THE SYRINX CAVITY: A CASE REPORT

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ABSTRACT

Aims: To present a rare syringomyelia case that necessitated a revision surgery because of a T-tube migration into the syrinx cavity. ***Case Report:*** A 53-year-old female patient was presented with progressive pain in the right arm and numbness in the neck. She had undergone decompression and stabilization surgery at the T6-T9 levels four years ago. One year later, she underwent a T-tube placement operation for syringomyelia. She remained relatively stable until the latest admission. A detailed neurological examination revealed no difference compared to her previous neurological condition. Computerized Tomography and Magnetic Resonance Imaging scans demonstrated that the syrinx had expended and the T-tube had migrated into the syrinx cavity. A revision was carried out, the migrated T-tube was removed through fenestration, and a new T-tube was placed. Her condition had significantly improved at follow-up, and the syrinx had markedly regressed. ***Conclusion:*** Syringosubarachnoid shunting operations might lead to rare complications such as T-tube migration, which necessitate revision surgery. Nearly complete relief of symptoms can be achieved with successful revision surgery. ***Keywords:*** Syringomyelia, revision, surgery

INTRODUCTION

Syringomyelia disease defined by the formation of fluid-filled longitudinal spaces (syrinx) in the spinal cord (1). These can expand and elongate over time, causing several symptoms that may vary depending on the area where the syrinx is applying pressure on the spinal cord (2). Therefore, patients may experience different combinations of the following symptoms: pain, weakness, stiffness in the back, shoulders, and extremities, and inability to distinguish hot and cold. Syringomyelia may occur due to hydrocephalus, Chiari malformation, tumors, spinal canal stenosis, and trauma, although many cases remain idiopathic (2, 3).

Posttraumatic syringomyelia (PTS) results from severe spinal cord injuries such as those from traffic accidents or falls from heights. PTS incidence varies between 1% - 7% (4). Patients are prone to neurological deterioration, for such cases, syringosubarachnoid shunting surgery is one of the treatments of choice (4,5). Syringosubarachnoid shunting operations, like other shunting procedures, might have many complications. We present a rare syringomyelia case that necessitated a revision surgery because of a migrated T-tube into the syrinx cavity.

CASE REPORT

A 53-year-old female patient was presented with progressive pain in the right arm and numbness in the neck. Her medical history included a car accident four years ago, causing a thoracic fracture-dislocation at T7-T8 resulting in paraplegia. She had undergone spinal surgery including the decompression and the stabilization of the T6-T9 levels (Figure 1). 10 months after the accident she was admitted with contractions in the arms and legs, syringomyelia ascending to the upper cervical region was found, and a thoracic syringosubarachnoid shunting surgery that included T-tube insertion into the syrinx cavity was performed (Figure 2). She remained relatively stable until her admission with progressive pain in the right arm and numbness in the neck.

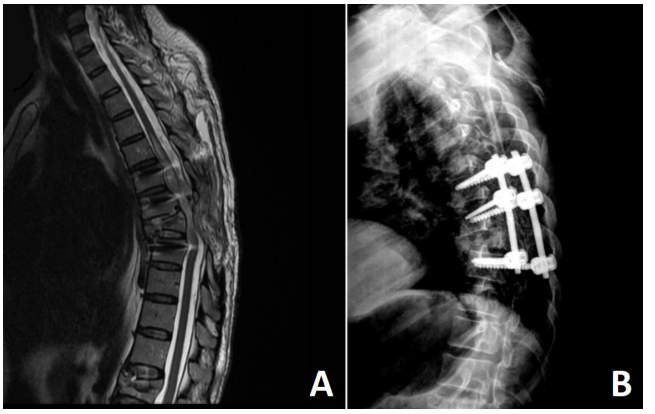

Figure 1: Images after the decompression and stabilization surgery of T6-T9 levels. A: Sagittal T2-weighted magnetic resonance image. B: Sagittal X-Ray image.

A neurological examination revealed no difference compared to her neurological condition following the spinal cord injury; there were no motor deficits in upper extremities, mild hypoesthesia in both arms and neck, total anaesthesia below the Th10 dermatome, and total paraplegia along with urinary and fecal incontinence.

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Computerized Tomography and Magnetic Resonance Imaging scans demonstrated that the T-tube had migrated into the syrinx cavity and the syrinx had progressed (Figure 3).

A revision surgery, including a central canal fenestration at the same location as the previous shunting surgery, was planned and carried out. During the revision surgery, the migrated T-tube was identified and removed through the fenestration (Figure 4). A new T-tube was placed through the same fenestration and fixed (Figure 5). The postoperative period was uneventful. At the sixth month follow-up, her symptoms had improved significantly, and the syrinx had markedly regressed (Figure 6).

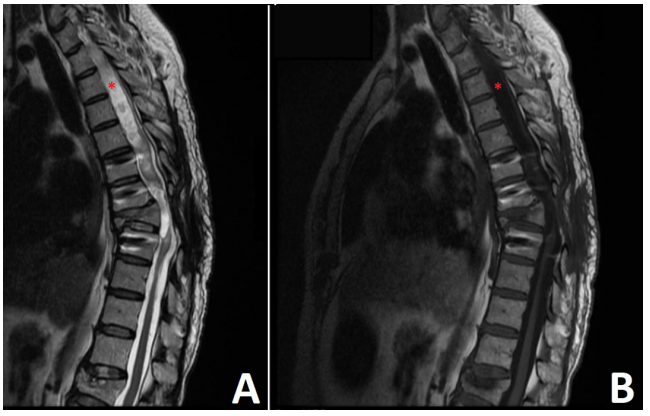

Figure 2: Syringomyelia that progresses to the cervical region (shown with asterisks). A: Sagittal T2 weighted magnetic resonance image. B: Sagittal T1 weighted magnetic resonance image.

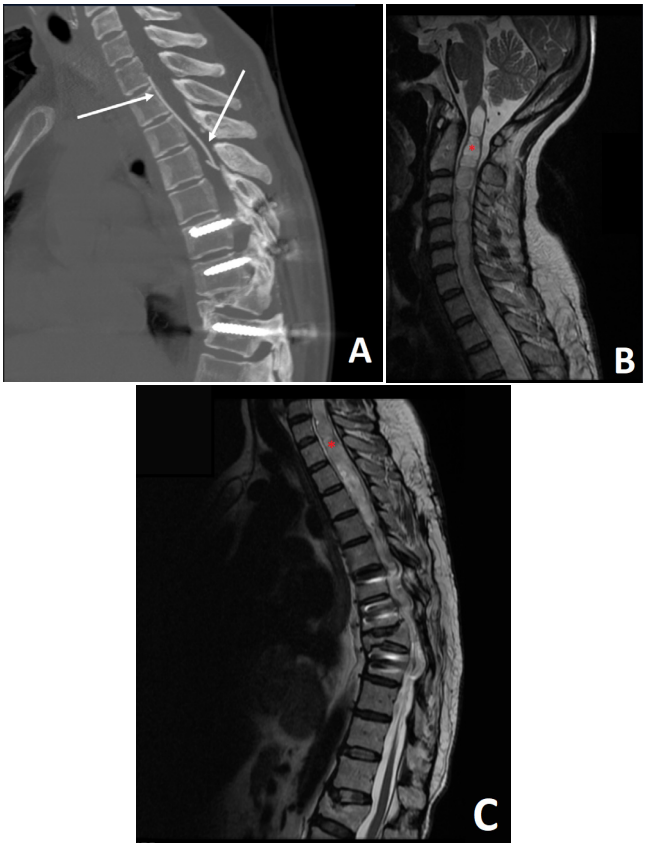

Figure 3: A: Reconstructed sagittal bone window CT scan image of the migrated T-tube into the syrinx cavity (shown with arrows). B, C: Cervical and thoracal sagittal T2 weighted magnetic resonance images of the syringomyelia that progresses to the upper cervical region (shown with asterisks).

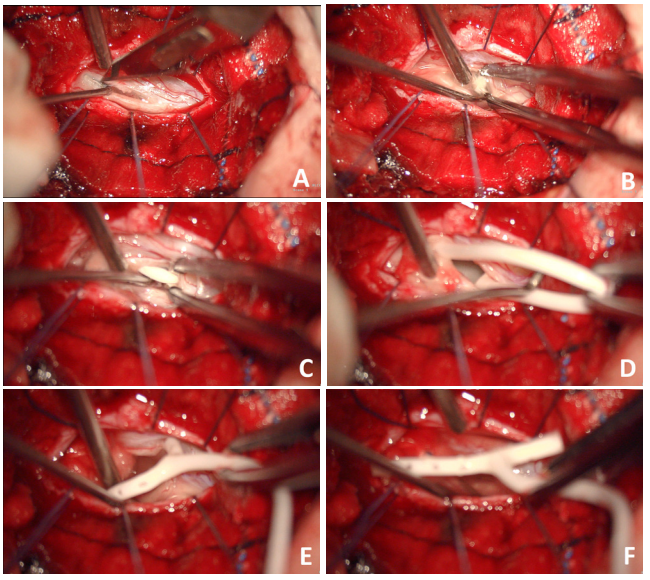

Figure 4: A-F: The stages of the operation in which the T-tube is removed.

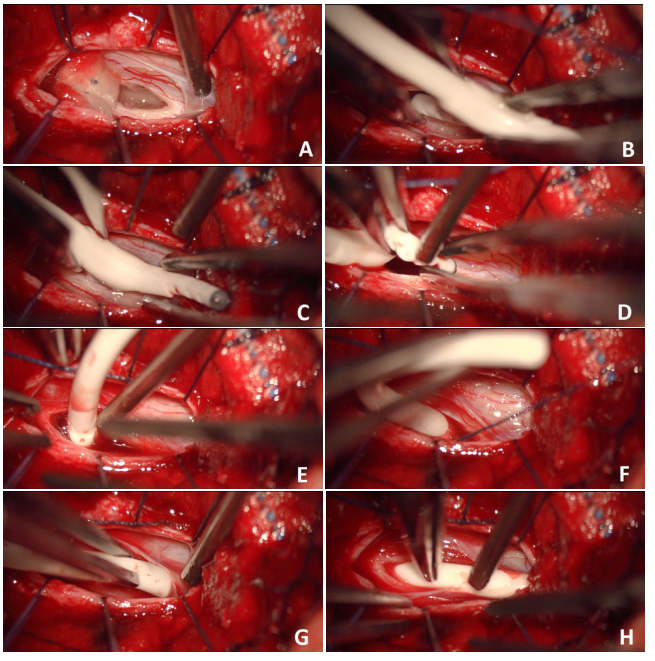

Figure 5: A-H: The stages of the new T-tube insertion process.

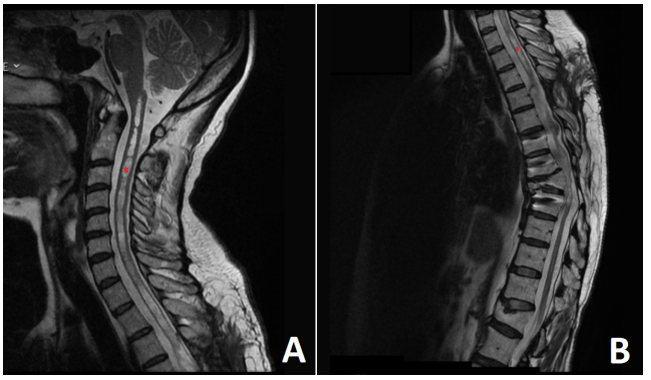

Figure 6: A, B: Cervical and thoracal sagittal T2 weighted magnetic resonance images of the syringomyelia regressed at 6th-month follow-up (shown with asterisks).

DISCUSSION

As syringomyelia is treated as a secondary phenomenon, rather than a primary spinal cord disease, not all cystic changes in the spinal cord are syringomyelia related. Therefore, the diagnosis of syringomyelia requires the identification of its cause (6). By definition, PTS is distinguished by an antecedent trauma.

An analysis of 138 patients with PTS by Krebs et al. (4) reported the syringomyelia in the cervicothoracic region in 58 patients (42%), in thoracic region in 50 patients (36.2%), in the cervical region in 19 patients (13.8%), and in the thoracolumbar region in 5 patients (3.6%). Furthermore, syringomyelia was detected at an average age of 42 years, a median of 15 years after the spinal cord injury. In the presented case, the patient was 53-year-old and diagnosed with syringomyelia in the thoracic region, ten months after the spinal cord injury.

There are various options for the surgical treatment of PTS, such as decompression, fenestration, bypass, and shunting procedures (7-10). For procedures that do not include the implantation of a tube, generally, the spinal cord is untethered from the dura by dismembering arachnoid adhesions, and one or multiple fenestrations are performed to the cyst from single or multiple openings (7). Hayashi et al. (8) investigated the results of a bypass surgery by connecting cranial and caudal normal subarachnoid spaces via tubes in 20 patients and reported that 12 patients showed clinical improvement, while four patients remained stable, and four deteriorated.

Shunting procedures include syringopleural, syringoperitoneal, and syringosubarachnoid shunting operations (5, 7-10). For syringomyelia, subarachnoid shunt is one of the treatments of choice and for patients with neurological deterioration, it is a safe and effective treatment (5). Karam et al. (3), in their study consisting of 27 PTS patients in total found that 10 of the 16 patients, on whom the performed surgery was the shunt alone, required revision surgery, while 3 of the 11 patients whose surgery included duroplasty, lysis of adhesions and shunting, required revision surgeries due to the lack of decrease in syringomyelia size and failure to improve the symptoms. Aghakhani et al. investigated the effectiveness of shunting and arachnoidolysis procedures in 34 patients. They reported that syringomyelia recovered or stabilized in 94% of the patients after arachnoidolysis and the spinal cord's untethering. They have also reported that shunting resulted in a higher risk of reoperation due to a higher recurrence (11).

In the presented case revision surgery was performed due to the T-tube's migration into the central canal. Since the patient had paraplegia, a more extensive fenestration and removal of the migrated T-tube were more comfortable to perform. Subsequently, a new T-tube was placed through the fenestration. During the follow-up, her symptoms had relieved significantly.

To conclude, a syringosubarachnoid shunt using a T-tube is an effective treatment option for PTS, although complications, including rare ones such as tube migration, might occur. In such cases, revision surgery is inevitable. In the revision surgery, when feasible, the new tube may be inserted using the same fenestration that was used to remove the dislocated tube. Successful revision surgery may improve the symptoms to a great extent.

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Author contributions: Concept: CY, ES, MYA, AÇ, ATA. Design: CY, ES, MYA, AÇ, ATA. Supervision: CY, ES, MYA, AÇ, ATA. Resources: CY, ES, MYA, AÇ, ATA. Materials: CY, ES, MYA, AÇ, ATA. Data collection and/or processing: CY, ES, MYA, AÇ, ATA. Analysis and/or interpretation: CY, ES, MYA, AÇ, ATA. Literature search: CY, ES, MYA, AÇ, ATA. Writing manuscript: CY, ES, MYA, AÇ, ATA. Critical review: CY, ES, MYA, AÇ, ATA.
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SQUAMOUS CELL CARCINOMA OF THE CAUDAL NASAL SEPTUM AND THE NASAL VESTIBULE: A CASE REPORT

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ABSTRACT

Aims: The nasal septum is an unusual place for malignant tumors to occur. The condition may be accompanied by non-specific symptoms that may cause delays in seeking medical care or may misguide the physician due to the condition's rarity. We hereby aim to present a rare case of a squamous cell carcinoma in a 65-year-old male patient with recently progressing symptoms. ***Case Report:*** A 65-year-old male patient was admitted to Private Keşan Hospital's Ear-Nose-Throat Department with swelling and wounds in the nose, and inability to breathe complaints. After the biopsy, pathological examination revealed moderately differentiated squamous cell carcinoma. The patient was operated with success; the mass was thoroughly dissected and a full-thickness skin graft from the left supraclavicular region was used in the reconstruction of defected areas. Recovery was uneventful due to early diagnosis and admission, with no relapse or cosmetic concern during monthly visits in the following years. ***Conclusion:*** As seen in this case, full-thickness skin grafts can be successfully used in intranasal and extranasal reconstructions, provided that they are obtained from areas with appropriate thickness. Early diagnosis and frequent monitoring are crucial in patients with squamous cell carcinoma since these tumors respond exceptionally well to treatment; although the recurrence rate is remarkably high.
Keywords: Nasal septum, squamous cell carcinoma, grafts

INTRODUCTION

Tumors of the nasal cavity and paranasal sinuses make up less than 3% of upper aerodigestive tract malignancies and less than 1% of all malignant tumors (1). Malignancies of the nasal septum are rare: only 9% of sinonasal malignancies are primary nasal septum malignancies (2). Even though their association with nasal septum malignancies is not yet fully known (partially because of the absence of standardized classification of nasal septum malignancies), smoking tobacco or occupational exposure to wood dust, petroleum products, chemicals used in nickel refining, leatherworking, textile, and isopropyl alcohol manufactory are among the risk factors for sinonasal adenocarcinomas (3-6).

Nasal septum tumors are generally seen in the 4th and 5th decades of males' lives (7). There is an increased risk of nasal carcinoma in tobacco smokers (8). Squamous cell carcinoma (SCC) is the most common malignant tumor of the nasal septum, which accounts for 66% of primary carcinomas of the nasal septum (6, 9).

Patients with SCC of the nasal septum may delay seeking medical care or their diagnosis may be delayed due to the non-specific symptoms that are similar to everyday rhinologic complaints. Patients present symptoms such as nasal obstruction, a nasal mass, recurrent epistaxis, pain, rhinorrhea, and facial edema. Common physical examination findings are nasal deformity, polyp, mucosal ulceration, and septal perforation (5, 9-11). Tissue biopsy is used for the diagnosis of nasal septum tumors (5).

There are various treatment approaches for nasal defects. Skin flaps from the areas adjacent to the nose such as cheeks and nasolabial sulcus can be used to repair the area (12). Median or paramedian forehead flaps can also be used (13). A full layer of skin cartilage graft can be taken from the auricle, especially in alar wing repairs that require skin and cartilage association (14). Repairment of the defected areas can be done with silicon septal buttons for defects that occur only in the septum, if there is no suitable tissue to cover the defected area, or if the patient especially requests it (15, 16).

In this article, we present the treatment approach to a rare case of SCC of the nasal septum.

CASE REPORT

A 65-year-old male patient was admitted to the Ear-Nose-Throat Department of Private Keşan Hospital with swelling and wounds in the nose, as well as inability to breathe. The patient had been a tobacco smoker for 30 years, smoking one pack a day, and had quit smoking 5 years ago. The patient stated that he had these complaints for 5-6 months, yet they progressed recently.

The patient went under ENT examination. The right nasal vestibule and cavity were observed as normal in the nasal examination but the left nasal cavity was filled with ulcerovegetant mass. A biopsy was recommended because of the patient's history and the appearance of the mass. The biopsy was performed under local anesthesia. Pathological examination revealed moderately differentiated SCC. The patient's head and neck examination, ultrasonography, and laboratory tests showed no pathological lymphadenopathy.

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Detailed information about his disease and the pathological result was given to the patient. The patient was told that surgery was required to remove the mass in his nose and how the surgery would be performed. An informed consent form was obtained from the patient. To not disrupt the blood flow to the nasal cavity, surgery under general anesthesia was decided, resulting in a successful functional reconstruction due to the size and diffuseness of the tumor. After the patient's tests and consultations were evaluated as suitable for anesthesia, the day of surgery was determined.

The operation was started as the patient went under general anesthesia, in the supine position with his head turned slightly to his right. The left nasal cavity was made visible after making a left lateral rhinotomy incision. It was observed that the tumor involved the left anterior part of the septum, the skin of the left nasal vestibule, and the left nasal ala (Figure 1). The incision, which had an adequate safety area from the tumor, was started from the left nasal vestibule.

When the septum was reached, the opposite mucosa was partly preserved, the mass was removed with the cartilage and dissected until the safe area behind was reached. Starting from the intact skin edge inside the ala, on the upper side, the tumor tissue was totally removed and continued downwards with sharp dissection. The tumor was approximately 15x20x10 mm in size. Surgical margins were marked with different suture materials. Where these margins coincided were written in detail before sending the samples to the pathology laboratory. Intranasal surgical margins were re-evaluated. The bleeding was controlled.

A left supraclavicular full-thickness skin graft was taken for the repairment of the septal, vestibular, and alar defect. The skin graft was 2x3 cm in size, the same as the defected area. The graft was sutured with an absorbable suture material inside the nose to the skin of the vestibule in the front, ala on the top and side, and septal mucosa on the back (Figure 2). The graft tissue was supported by placing an absorbable hemostatic gelatin sponge in the nasal cavity. There were no preoperative or postoperative complications.

No problem with the nutrition of the graft was observed. The patient was taken to his bed in good condition. Following the graft healing, no intranasal or extranasal problems were observed. The nasal passage continued to be completely open. There was no cosmetic problem in the nasal appearance (Figure 3).

Histopathological examination of the removed tissue confirmed moderately differentiated SCC. All of the surgical margins marked were reported as tumor-free and safe. The supraclavicular area (donor area) where the skin graft was taken, also healed without any problem.

Figure 1: Intraoperative image of the tumor. Tumor involves the left anterior part of the septum, the skin of the left nasal vestibule, and the left nasal ala.

Following the discharge of the patient, a detailed epicrisis was written and sent to the oncology clinic, with the pathology reports attached. As a result of the patient's oncological examination, it was stated that the surgery performed was sufficient, and did not require any additional treatment or procedure.

The patient was called for monthly follow-up visits during the first year after the operation and was followed up for both local relapse and metastasis. Local areas and the areas with high drainage possibility were followed by ultrasonography in terms of lymphadenopathy. In the second year, he was called and followed up every three months. The patient completed his third year without local relapse and metastasis. During all these follow-ups, the patient had no clinical complaints.

Figure 2: Placement of the supraclavicular skin graft to the nose.

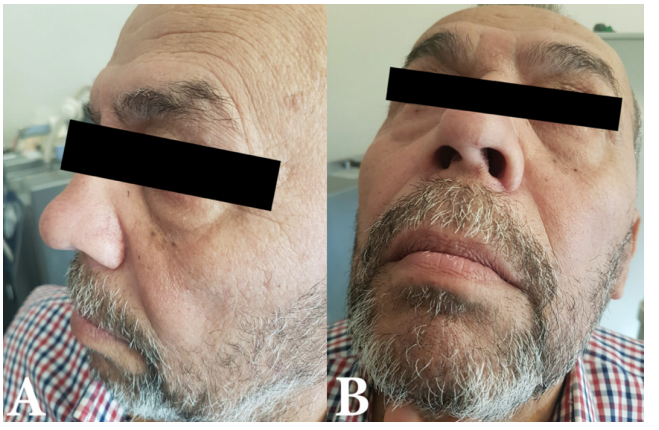

Figure 3: A, B: Patient's postoperative appearance.

DISCUSSION

To the best of our knowledge, fewer than 400 nasal septum malignancies had been reported up until the year 2010, making it quite a rare case (5). The diagnosis of nasal septum malignancies is often delayed due to the nonspecific symptoms. Tissue biopsy is the most straightforward way for diagnosis (5). Our patient came with nonspecific symptoms such as swelling and wounds in the nose, and an inability to breathe. With further examination an ulcerovegetant mass was observed in the left nasal cavity, then it was decided for the patient to have a biopsy. The final diagnosis after the pathological examination was moderately differentiated SCC. Correct surgical excision is the gold standard for the diagnosis and treatment of SCC (17). Our patient had surgery under general anesthesia and the tumor was removed successfully.

After the surgery, septal, vestibular, and alar defects were seen. Various treatments can be applied to nasal defects. The case's specificities, patient's age, and medical history, the experience of the surgeon are the criteria in determining the appropriate way of reconstruction. Flaps of the cheek, nasolabial sulcus, median, and paramedian forehead or grafts obtained from conchal cartilage can be used for the repairment of nasal septal defects (12-14). Small or medium-sized defects can also be repaired with the advancement flaps, which can be applied in all anatomic regions of the nose (18). Silicon septal buttons can be used if there is no suitable tissue to cover the affected area (15, 16). In total or subtotal nasal reconstructions, forehead flaps may be considered primarily. However, since the face is the most striking part in terms of cosmetics, choosing a donor site further away from the face, and which will not cause cosmetic problems, will increase patient satisfaction. Refined aesthetic outcomes and preserving nasal functions are crucial in a nasal operation, thus the surgeon should decide the best and most suitable method for the patient. Sapthavee et al. (19) stated that skin grafts provided aesthetic outcomes comparable to those of local flap procedures. In this case, since the mucosal and cartilage tissue defects that occurred after the removal of the tumor were large, a large and solid tissue was required for repairment. Therefore, a full-thickness skin graft from the supraclavicular area was successfully used for the reconstruction of the defected areas.

When the diagnosis is made in the early stage, tumors respond well to treatment. Close and frequent monitoring after treatment is crucial in nasal septum malignancies because of its high local recurrence rate (7). Our patient made monthly follow-up visits during the first year after the operation and visited every three months in the second year. No local relapse, metastasis, or clinical complaints were observed for three years. This good prognosis and healing process of the patient may be a result of early diagnosis.

Our patient was a former smoker for 30 years and smoked around 1 cigarette pack per day. This is a risk factor for cancers, including nasal carcinomas. Bosch et al. (20) reviewed 40 patients with nasal cancer over 15 years. There was an association between patients who smoked from an early age (median age=14 years) and nasal cancer. Another study also found out that the highest risk of nasopharyngeal cancer was observed among men who have smoked for 30 years or more (21). Direct contact of the tobacco smoke on nasal mucosa may explain the increased incidence.

Due to the rarity of nasal septum malignancies, the understanding of the disease is still limited. We believe that this case report will provide physicians a different perspective and make a contribution to the literature.

In conclusion, full-thickness skin grafts can be successfully used in intranasal and extranasal reconstructions as long as they are obtained from the areas with appropriate thickness. Early diagnosis and frequent monitoring are crucial in those patients with squamous cell carcinoma, as these tumors respond exceptionally well to treatment but the recurrence rate is remarkably high.

Ethics Committee Approval: N/A
Informed Consent: Verbal informed consent was obtained from the patient.
Conflict of Interest: The authors declared no conflict of interest
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1. I have read, and understood the Participant Information Sheet dated _____
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3. I understand that the case report will be published without my name attached and researchers will make every attempt to ensure my anonymity. I understand, however, that complete anonymity cannot be guaranteed.
4. I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Name of Participant: _____

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