E-ISSN: 2548-0030
ISSN:2148-4724

TMSJ

TURKISH MEDICAL STUDENT JOURNAL

Volume: 11 | Issue: 2 | June 2024

https://turkmedstudj.com/

galenos yayinevi

TMSJ

TURKISH MEDICAL STUDENT JOURNAL

THE OFFICIAL JOURNAL OF
TRAKYA UNIVERSITY SCHOOL OF MEDICINE

Citation Abbreviation: Turk Med Stud J

VOLUME 11 - ISSUE 2 - June 2024

Published three times a year

Free access to the journal's website: *https://turkmedstudj.com/*

Manuscript Submission: *https://tmsj.manuscriptmanager.net/*

Editorial Office
Address: Trakya Üniversitesi Tıp Fakültesi
22030 Edirne, Türkiye
Phone: +90 (284) 235 76 53
E-mail: tmsj@trakya.edu.tr

Printing at: Trakya Üniversitesi Matbaası
Edirne Teknik Bilimler M.Y.O Sarayiçi Yerleşkesi,
22020 Yeni İmaret, Edirne, Türkiye
Phone: +90 (284) 224 02 83
Printing Date: June 2024
ISSN: 2148-4724 E-ISSN: 2548-0030

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The journal is printed on an acid-free paper and published online.

Owner: Trakya University

Responsible Manager: Eylül Şenödeyici

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TURKISH MEDICAL STUDENT JOURNAL

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TURKISH MEDICAL STUDENT JOURNAL

Editorial

DOI: 10.4274/tmsj.galenos.2024.130624

Dear Readers,

It is with great pleasure that we present the second issue of 2024.

For the first time in our journal's history, the number of our external editors exceeds that of our editors in Trakya University, our home institution. With our editorial board now spanning four countries and twelve institutions, our mission to encourage medical students to be involved in scientific research expands beyond physical borders. Our journal's stature in the scientific publishing community reaches new heights as it continues to inspire the upcoming generation of physician-scientists. Praised by many medical students and renowned scientists alike, Turkish Medical Student Journal is still the sole indexed medical student journal in our country. Our decade-long experience and dedication to inspire are the very pillars of our unmatched status in the Turkish scientific community, and we will continue to support and encourage scientific research among medical students for many years to come.

Eylül Şenödeyici, Editor-in-Chief

TMSJ
TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2024;11(2):32-9
DOI: 10.4274/tmsj.galenos.2024.2024-5-1

REVIEW

REVOLUTIONIZING LUNG CANCER CARE: THE MULTIFACETED APPROACH OF ARTIFICIAL INTELLIGENCE, LIQUID BIOPSIES, AND CIRCULATING TUMOR DNA IN SCREENING, DIAGNOSIS, AND PROGNOSIS

Ahmet Arda Ünal, Yiğit Yazarkan, Gamze Sönmez, Ateş Kutay Tenekeci

Hacettepe University School of Medicine, Ankara, TÜRKİYE

ABSTRACT

Screening for lung cancer has been seeing new developments, with a focus on emerging technologies and the integration of artificial intelligence. While low-dose computed tomography shows promise in reducing mortality rates, challenges, especially regarding screening guidelines and radiation exposure, have been known for a long time. Additionally, discrepancies in screening methods across countries have been challenging the necessity of standardized protocols and cost-effective approaches. Liquid biopsy, particularly circulating tumor DNA analysis, presents a promising non-invasive method for early lung cancer detection and monitoring. Recent studies highlight its potential in detecting genetic mutations, predicting treatment responses, and monitoring minimal residual disease. However, standardization and clinical validation are crucial for widespread adoption. Integration of artificial intelligence into lung cancer screening holds significant promise for enhancing accuracy and workflow efficiency, reducing the burden on radiologists. Successful implementation necessitates validation, regulatory approval, and ethical considerations. Collaborative efforts among clinicians, data scientists, engineers, and policymakers are crucial for translating research into practice, ultimately maximizing the impact of artificial intelligence on patient outcomes. Continued research, validation, and collaboration are imperative for realizing the full potential of these advancements and addressing challenges in clinical implementation.

Keywords: Artifical intelligence, circulating tumor DNA, early detection, liquid biopsy, lung cancer

INTRODUCTION

Lung cancer is a serious health condition affecting millions worldwide, challenging both medical professionals and patients alike. As one of the most prevalent and deadly cancers globally, it warrants a thorough examination to understand its complexities, advancements in treatment, and the evolving landscape of hope for those affected (1). Each day, around 340 individuals succumb to lung cancer, a staggering figure nearly 2.5 times higher than the fatalities from colorectal cancer, the second-leading cause of cancer-related deaths (1). According to Cancer Statistics, in 2024, approximately 81% of the 125,070 lung cancer deaths will be directly attributed to cigarette smoking, with an additional 3,500 deaths linked to second-hand smoke exposure (1, 2). While smoking is recognized as a significant risk factor for the development of lung cancer, the incidence of lung cancer in individuals who have never smoked remains steady or is on the rise (3). There are some other risk factors such as marijuana use, asbestos exposure, and electronic cigarettes (4, 5). The connection between marijuana use and lung cancer is uncertain because of contradictory findings, while the association with electronic cigarettes remains unclear, partly due to the influence of prior or concurrent cigarette use and the absence of long-term data (4). Asbestos exposure combines synergistically with tobacco use, leading to higher rates of lung cancer compared to either risk factor alone (5). Additional risk factors include exposure to radon, hormonal factors, and infectious factors (5). Chronic obstructive pulmonary disease

Address for Correspondence: Ahmet Arda Ünal, Hacettepe University Faculty of Medicine, Ankara, TÜRKİYE
e-mail: ahmetunal18@hacettepe.edu.tr
ORCID iD of the authors: AAÜ: 0000-0001-7156-344X; YY: 0009-0000-8989-5207; GS: 0009-0001-3488-0283; AKT: 0009-0007-6224-945X
Received: 06.05.2024 Accepted: 27.06.2024

Cite this article as: Ünal AA, Yazarkan Y, Sönmez G et al. Revolutionizing lung cancer care: the multifaceted approach of artificial intelligence, liquid biopsies, and circulating tumor DNA in screening, diagnosis, and prognosis. Turk Med Stud J. 2024;11(2):32-9.

and a positive family history are also linked to lung cancer, as well as the tobacco exposure (5).

The biological mechanisms driving lung cancer are intricate, and the tumors exhibit significant variability, making their development still not fully comprehended (6). Recent advancements in understanding pathways, detection technologies for actionable genetic abnormalities, and the development of new medications have enabled physicians to customize treatment options. In lung adenocarcinoma, several significant pathways that can be targeted have been recognized, including epidermal growth factor receptor (EGFR), phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin, RAS-mitogen-activated protein kinases, and neurotrophic tropomyosin-receptor kinase/ROS1, anaplastic lymphoma kinase, mesenchymal-epithelial transition factor, human epidermal growth factor receptor 2 (HER2) pathways (7, 8) (Figure 1). Numerous medications targeting these pathways have been created and have demonstrated clinical advantages (9). However, despite the disease control provided by targeted therapy in non-small cell lung cancer (NSCLC), tumors inevitably develop resistance to drugs (9). Understanding the mechanisms of resistance and creating combination therapies are crucial for enhancing treatment outcomes (9). Despite challenges, in recent years, the use of immune-checkpoint inhibitors, primarily monoclonal antibodies that hinder the inhibitory immune checkpoints cytotoxic T-lymphocyte associated protein 4 (CTLA4) and programmed cell death protein 1 (PD-1), along with its ligand programmed cell death protein ligand 1 (PD-L1), have transformed the approach to treating advanced-stage NSCLC (7). These treatments offer long-lasting disease management for specific patients, whether utilized independently or in conjunction with other therapies, reshaping the treatment landscape (7).

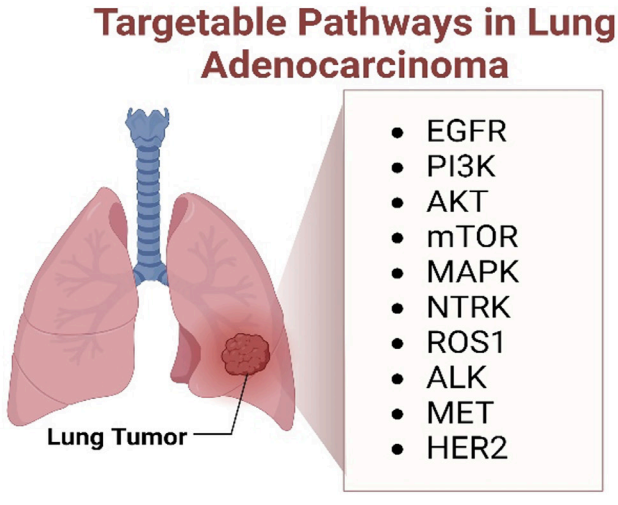

Figure 1: Targetable pathways in lung adenocarcinoma. Created with BioRender.com.
EGFR: Epidermal growth factor receptor, PI3K: Phosphatidylinositol 3-kinase, mTOR: Mammalian target of rapamycin, MAPK: RAS-mitogen-activated protein kinases, NTRK: Neurotrophic tropomyosin-receptor kinase, ALK: Anaplastic lymphoma kinase, MET: Mesenchymal-epithelial transition factor, HER2: Human epidermal growth factor receptor 2

In this review we aim to discuss the latest developments in the diagnosis of lung cancer, worldwide screening programs, and the role of artificial intelligence (AI).

Lung Cancer Screening in the World

Early detection through screening holds the promise of reducing lung cancer mortality by facilitating timely intervention, enabling curative treatments, and improving overall survival (OS) rates. Numerous research endeavors have delved into the significance of low-dose computed tomography (LDCT), with the most extensive being the National Lung Screening Trial (NLST) (10-14). In 2011, this trial revealed that there was a 20% reduction in lung cancer mortality (with a 95% confidence interval ranging from 6.8% to 26.7%) (10, 14). More recently, another randomized clinical trial, Nederlands Leuvens Screening Onderzoek (NELSON), concluded that there was a notable decrease in lung cancer mortality among individuals who received volume computed tomography (CT) screening compared to those who did not undergo any screening (11). A recent cohort study by Silvestri et al. (12) found that there was a notable shift towards detecting early-stage lung cancer, which was significant. However, adherence to lung cancer screening (LCS) was lacking, which likely influenced the lower-than-anticipated rate of cancer detection (12).

Screening for lung cancer is most beneficial when focused on individuals with a high risk of developing the disease, and there are various methods available to pinpoint these high-risk individuals. The NLST and NELSON studies employed straightforward criteria to identify individuals at high risk (10, 11). NLST targeted individuals aged 55-74 years who had smoked at least 30 pack-years and, if they quit, had done so within the last 15 years (10). NELSON focused on individuals aged 50-74 years who had a history of smoking more than 15 cigarettes per day for over 25 years or over 10 cigarettes per day for over 30 years, with recent quitters within the past 10 years also included (11).

In any screening program, it is crucial that the advantages outweigh the drawbacks. There are unique challenges specific to LDCT LCS, such as effectively stratifying the risk of potential participants, managing radiation exposure, and handling incidental findings. Moreover, for a screening program requiring extensive infrastructure, considerations of cost-effectiveness and workforce are crucial. While data on these matters exists within LCS trials, variations in methods and healthcare systems among studies make it challenging to directly apply results across different screening populations. The introduction of different guidelines aims to standardize the reporting and handling of findings from screenings, potentially lowering both harms and expenses (13).

Screening methods may differ in different countries (15). In Japan, systematic screening has been provided to all individuals within the specified target demographic (men and women aged 40-79 years) using chest X-rays and sputum cytology (16). Despite randomized controlled trials conducted in the United States of America and Europe indicating that chest radiography

is ineffective and that LDCT is effective in reducing mortality, Japan continues to advocate for X-rays and sputum cytology (16). LCS methods among countries and their advantages/disadvantages are shown in Table 1.

Current Methods in Lung Cancer Screening

In 2013, the United States Preventive Services Task Force (USPSTF), largely influenced by findings from the NLST, endorsed yearly LDCT screening for individuals aged 55 to 80 years with a minimum 30 pack-year smoking history, regardless of current smoking status or having quit within the previous 15 years (17). These guidelines were broadened following the more recent NELSON trial outcomes, which demonstrated reduced lung cancer mortality with LDCT in a population with a lower overall risk, as well as insights gleaned from sophisticated modeling studies (11). The current USPSTF recommendation for LCS now extends to adults aged 50 to 80 years with at least a 20 pack-year smoking history, including current smokers or those who quit within the past 15 years (18). In 2022, the Centers for Medicare and Medicaid Services assessed the evidence for Medicare coverage of LCS, adopting similar eligibility criteria, albeit with a slightly lower upper age limit of 77 years instead of 80 (19).

The current standards not only widen the scope of eligibility and accessibility for LCS compared to the 2013 guidelines but also demonstrate potential for improved health outcomes at the population level (2). Computational modeling indicates that annual screening of individuals meeting the revised USPSTF criteria could yield a 13.0% decrease in lung cancer mortality, preventing 503 lung cancer fatalities and accumulating 6918 additional life-years per 100,000 individuals aged 45 to 90 years over their screening lifespan (3). By contrast, adherence to the 2013 USPSTF recommendations was projected to achieve a 9.8% reduction in lung cancer mortality, averting 381 lung cancer-related deaths and accumulating 4882 extra life-years per 100,000 individuals in the same demographic (20, 21).

In 2016, the Ministry of Health (MoH) in Türkiye organized an LCS workshop, highlighting the significance of community screening due to the epidemiological profile of lung cancer in the country (22). Despite consensus on the importance of screening, the feasibility of a nationwide program was questioned due to occupational and environmental exposures, as well as concerns about false-positive results and overdiagnosis, particularly in regions endemic to tuberculosis infection (23). Consequently, it was decided to initiate a regional pilot study in the Aegean region (23). As of now, Türkiye does not have an official LCS program in place for high-risk or former smokers (23).

Despite the documented clinical benefits of LDCT LCS recommended by the USPSTF, reports indicate significant underutilization (24). The lack of widespread adoption of LDCT screening since its inception stems from a multitude of factors. Following the release of the NLST and NELSON findings and subsequent guideline recommendations, LCS has remained

Table 1. Lung cancer screening methods among countries and their advantages/disadvantages (15).

Country	Screening method	Advantages	Disadvantages
Japan	X-ray to men and women aged 40-79 years	High participation to screening (50% of eligible population) Lower dose of radiation	Population's negative attitude towards radiation X-ray based screening needs confirmation with CT and this leads to both extra cost and radiation
United States of America	Low dose CT to 50-80 years of age with a 20 pack-year smoking history	High number of CT machines in the country Physicians are educated about screening	Low participation due to its cost (5% of eligible population) No discussion with GPs after the screening
China	Low dose CT to 50-74 years with a 20 pack-year smoking history who are current smokers or quit in the past 5 year	Low cost of CT in the country High awareness towards lung cancer in the country Free access to any hospital in the country	Low trust to doctors in the society High number of patients living in rural areas Low number of CT machines in the rural parts of the country.
South Korea	Low dose CT to current smokers aged 54-74 years with a 30 pack-year smoking history	Political support towards screening Low cost of the CT	Low participation of patients due to "lack of time" Physician awareness is low about screening
Canada	Low dose CT to 55-74 years of age who are currently or have previously smoked and have a 20 pack-year smoking history	Government support towards screening Low cost of CT High number of CT machines in the country	Lack of knowledge among citizens due to its newer implantation Lack of data about cost, participation rate etc.

CT: Computed tomography, LCS: Lung cancer screening, GP: General practitioner

a subject of contention among healthcare providers due to uncertainties surrounding its applicability, associated costs, benefits, and false positive rates (25).

Primary care providers' role in cancer screening, including assessing eligibility and making referrals, contributes to the low rate of LCS (26, 27). Challenges such as limited knowledge of LDCT screening and competing patient health concerns hinder referral rates, along with inconsistent recommendations from primary care societies (26, 27). Additional concerns surrounding LCS involve issues regarding insurance coverage and cost-effectiveness. LDCT has been determined to be cost-effective, as evidenced by seven separate analyses showing an effectiveness ratio of US $100,000 or less per quality-adjusted life years gained (28). Patients' psychosocial characteristics and attitudes towards cancer screenings also contribute significantly to underutilization. LCS presents unique challenges compared to established cancer screenings due to the perceived stigma surrounding it as a disease primarily caused by smoking, which can deter individuals from seeking screening (29). Therefore, considering these negative aspects and utilizing evidence-based data, the development of new screening methods could enhance the effectiveness of screening programs.

The Newest Methods in Lung Cancer Screening

Liquid Biopsy

Liquid biopsy is a recent technology in oncology, especially important in the treatment of lung cancer, the leading cause of cancer-related deaths globally (1). This new non-invasive approach analyzes circulating biomarkers in the blood, such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomes and microRNAs, providing vital information (30). This method allows us to understand tumor behavior, which can alter treatment strategies tailored to the individual characteristics of each cancer patient. The utilization of liquid biopsy in lung cancer is important, given the disease's typical late diagnosis and poor prognosis. With early detection of cancer through sensitive identification of ctDNA or other biomarkers, liquid biopsy has the potential to initiate early treatment, significantly improving patient survival rates. As liquid biopsy technology advances, it becomes increasingly precise, cost-effective, and integral to standard cancer care protocols. The capacity of liquid biopsy to detect a wide range of biomarkers, such as mutations, rearrangements, methylations, and changes in gene expression, provides an integrated view of the genetic landscape of cancer. These developments enhance lung cancer therapy, moving toward a more targeted, effective, and minimally invasive approach to managing one of the most challenging diseases in modern medicine (30).

Circulating Tumor DNA

With these new technologies, ctDNA via liquid biopsies represents a transformative approach that augments traditional cancer detection and monitoring methods. This non-invasive technique provides genomic profiling of tumors, which is necessary in the era of precision medicine (31). Utilizing ctDNA analysis shows promising data in several key areas: early detection of malignancy and minimal residual disease (MRD), assessing the dynamic genetic landscape of tumors in response to therapy, and predicting responses to immunotherapy (31). The ability of ctDNA testing to detect genetic mutations and alterations in blood samples allows oncologists to overcome the limitations of standard tissue biopsies. Moreover, liquid biopsies offer an integrated view of tumor heterogeneity and provide insights into tumor genetics' evolutionary pathways, thereby allowing for personalized treatment adjustments that have the potential to improve patient outcomes (31). With their promising applications, the sensitivity and specificity of ctDNA assays require standardization and clinical validation to realize their potential in routine clinical practice (31).

A recent study investigated the role of ctDNA as both a diagnostic and a prognostic tool in lung cancer (32). It included 211 individuals suspected of having lung cancer, with 192 ultimately participating (32). These participants, who had an average age of 63 years, provided blood samples before surgery (32). The results showed the test had a sensitivity of 75% and a specificity of 89%, revealing it has reasonable specificity but moderate sensitivity for diagnosing lung cancer (32). The test's positive predictive value was 98%, highlighting its power in the detection of cancer presence (32). However, its negative predictive value was only 35%, indicating a limitation in excluding cancer when no ctDNA is found (32). A meta-analysis from Qiu et al. (33) analyzed data from 27 studies involving 3110 participants, mainly from Asia, to assess the effectiveness of ctDNA in detecting EGFR mutations in NSCLC. The results showed that the ctDNA test has a sensitivity of 62% and a specificity of 95.9%. This supports ctDNA as a non-invasive alternative to tissue biopsy for guiding EGFR-Tyrosine kinase inhibitors therapy in NSCLC (33).

Minimal residual disease in NSCLC can be defined as micrometastases that remain after initial therapy (34). MRD may be the cause of a metastatic relapse at other locations. Although MRD monitoring and detection are frequently used in patients with hematological malignancies, they can be difficult to sample in patients with solid tumors because of the low concentrations of CTCs, or components released into the bloodstream by cancer cells (34). A meta-analysis evaluates the effectiveness of ctDNA for detecting MRD in lung cancer (35). The meta-analysis investigated ctDNA MRD detection methods, including tumor-informed and tumor-agnostic approaches, across different stages of lung cancer (35). Findings showed moderate sensitivity and high specificity for ctDNA MRD predicting lung cancer recurrence (35). A recent study by Chen et al. (36) explored the application of ctDNA to detect gene mutations in patients with early-stage NSCLC through targeted sequencing. Results showed that this non-invasive method is especially beneficial in early-stage NSCLC, where traditional biopsy techniques may fail (36). The research demonstrated that ctDNA screening has a sensitivity of 53.8% and a specificity of 47.3% (36).

Circulating tumor DNA can also be used to monitor the efficacy of immunotherapy for NSCLC (37). A study was designed with 28 patients who received PD-1 or PD-L1 inhibitors (37). Then, next-generation sequencing was used to measure changes in ctDNA, defined by a greater than 50% reduction in the mutant allele fraction from the baseline, confirmed by a subsequent measurement (37). Notably, ctDNA provided an early indication of treatment response, with a median time to initial response of 24.5 days compared to radiographic responses, which were 72.5 days, illustrating ctDNA's faster detection capacity (37). Furthermore, patients demonstrating a ctDNA response experienced significantly extended progression-free survival, with a hazard ratio of 0.29, and improved OS, with a hazard ratio of 0.17 (37).

DNA methylation alterations, together with other tumor-derived characteristics, are emerging as promising biomarkers for lung cancer (38, 39). A recent study focuses on developing and validating a ctDNA methylation-based assay to aid in the early detection and diagnosis of lung cancer (40). This case-control study has participants from various clinical centers, including patients with lung cancer, benign lung disease, and healthy individuals (40). A quantitative polymerase chain reaction assay, LunaCAM, was created in two models: LunaCAM-S for screening, prioritizing sensitivity, and LunaCAM-D for diagnostic aid, emphasizing specificity (40). The validation of these models involved profiling DNA methylation on 429 plasma samples, yielding significant markers capable of distinguishing lung cancer from benign diseases and healthy conditions with high accuracy (40). In one meta-analysis of the diagnostic performance of methylated ctDNA for lung cancer detection, data from 33 studies were analyzed to assess the effectiveness of methylated ctDNA as a diagnostic biomarker (41). The results revealed variability in sensitivity and specificity across different studies, with a summary sensitivity estimate of 46.9% and a summary specificity estimate of 92.9% (41). The diagnostic odds ratio was 11.5, indicating the diagnostic power of methylated ctDNA in distinguishing lung cancer cases from controls (41). The area under the hierarchical summary receiver operating characteristic curve was 0.81, demonstrating sufficient diagnostic ability (41).

Circulating tumor DNA detection tests also predict the survival outcomes of patients (42). Assaf et al. (43) used ctDNA to predict survival outcomes in patients with metastatic NSCLC. This phase 3 IMpower150 trial involves 466 patients and assesses ctDNA at five different time points using a machine learning model to predict OS (43). The model demonstrated the capability to stratify patients into high-risk and low-intermediate-risk groups based on ctDNA levels, with differences in median survival times (43). Patients identified as high-risk based on early ctDNA levels had a median OS of 7.1 months, compared to 22.3 months for those in low-intermediate-risk categories (43). ctDNA screening can also be used in disease monitoring, and it has shown promising results (44).

Artificial Intelligence

Artificial intelligence (AI) is becoming an important aspect in the field of lung cancer detection (45, 46). AI algorithms that have been trained on different datasets of medical images can both help radiologists and clinicians, easing their workload and improving patient care (45, 46). AI models can be used in various ways to detect lung cancer (45, 46).

Low-dose CT scans (LDCT) are critical for reducing mortality in lung cancer, however, repeated CT scans can have some radiation-associated risks (47, 48). Deep-learning reconstruction (DLR) offers a novel approach by extracting true information from low-quality images, improving image quality without trade-offs (47, 48). These models were used during the Coronavirus Disease of 2019 pandemic (49). Another model, ClariCT.AI (ClariPI), shows promising results in post-processing imaging, particularly for ultra-LDCT (50). DLR is becoming a reconstruction method for LDCTs, improving accuracy in measuring lung nodule sizes while reducing radiation exposure, especially for long-term follow-up patients (50).

Artificial intelligence used in this field is generally called Computer-aided Diagnostic (CAD) systems. The CAD system plays a critical role in LCS, particularly with the increasing use of LDCT for early detection (51). These systems rely on radiological images, typically collected from public databases like LIDC-IDRI, LUNA16, ELCAP, and ANODE09 (51). These public databases provide a diverse range of CT scans with lung nodules, facilitating the development and training of CAD algorithms. LIDC-IDRI, established by the National Cancer Institute, is a widely utilized database containing chest CT scans annotated by expert radiologists. LUNA16 is another publicly available dataset specifically designed for training deep learning algorithms for lung nodule detection. CAD systems help radiologists by reducing observational errors, providing a second opinion, and improving the diagnostic process (52, 53).

Convolutional neural networks (CNNs) are examples of CAD systems that were developed in a multidisciplinary fashion, demonstrating high sensitivity in nodule detection and aiding specialists in the diagnostic process (46). Chi et al. (54) developed a CNN-based system achieving a precision of 88%, a sensitivity of 89%, and a specificity of 96%. Nasrullah et al. (55) utilized CMixNet, achieving a sensitivity of 94% and a specificity of 91%, analyzing nodules for classification as benign or malignant. Other approaches, combining CNNs and data augmentation, achieved an accuracy of 95% (45, 46). Hybrid networks combining CNNs with novel three-dimentional (3D) frameworks like IR-UNet++ feature extraction techniques can achieve remarkable accuracy in the categorization of lung histopathology images (45, 46, 56). Cai et al. (57) employed MaskRCNN for nodule identification with a sensitivity of 88.70% and provided segmentation and 3D visualization capabilities. Manickavasagam et al. (58) developed a CNN with five convolutional layers that reached high accuracy, sensitivity, and specificity.

After nodule detection, lung nodule segmentation presents challenges due to its small size and proximity to edges or vessels (59). Various segmentation systems, like U-Net and fully CNN, are aiming to improve accuracy in that area (59). Different algorithms were being developed for segmenting a lung nodule (59). These models prioritize enhancing nodule boundaries, especially near blood vessels and the pleural tissue (59). Pezzano et al. (60) introduced a U-Net-based model with the Multiple Convolutional Layers module, improving boundary definition. Dong et al. (61) incorporated voxel and shape heterogeneity properties, capturing variations in gray voxel values effectively. Al-Shabi et al. (62) achieved outstanding results compared to other models, with an area under the curve of 95.62%. These models are making significant advancements in lung nodule segmentation, particularly in challenging cases. By recognizing these subtle patterns and abnormalities that may not be seen with the human eye, AI systems hold the potential to revolutionize LCS and diagnosis (46).

Virtual biopsy methods that use the spatial and temporal heterogeneity of the tissues surrounding the solid tumors are currently being developed. These virtual biopsy methods use deep learning methods to detect non-invasive radiomic signals or biological features related to clinical outcomes (63, 64). The main goal is to replace surgical biopsies and histopathologic analysis. Additionally, these techniques are advancing the development of a personalized medical system. At the Mayo Clinic in Rochester, Lee et al. (65) developed a machine-learning technique known as Computer-Aided Nodule Analysis and Risk Yield (CANARY). CANARY discovered nine distinct radiomic signals defining the lung cancer spectrum (65). CANARY as a virtual biopsy technique correlates directly with adenocarcinoma invasion (65). In their study, Lafata et al. (66) discovered that tumors exhibiting greater homogeneity and attenuation on CT imaging were associated with detectable ctDNA TP53 mutations and stable alterations in ctDNA content during the early stages of therapy.

These models are not only used for nodule detection and segmentation but also for clinical outcomes. AI models were being developed to interpret medical data, predict tumor metastasis, guide treatment decisions, and assess patient prognosis. These new models are also offering personalized medicine approaches to patients (45, 46). They are aiding clinicians in the management, diagnosis, and prediction of treatment outcomes. A model developed by Pérez-Morales et al. (67) estimated lung cancer patients' outcomes when the tumor was identified during screening by using radiomic properties from the intratumoral and peritumoral regions. Yu et al. (68) created a model to predict the mortality risk of patients after first-line treatment by using data from patients who had undergone surgery for stage I NSCLC. Cousin et al. (69) conducted a study aiming to identify a CT-based delta-radiomics signature for distinguishing individuals who are likely to benefit from PD-1/PD-L1 inhibitors in advanced or recurrent NSCLC.

Interdisciplinary research efforts combining radiomics, digital pathology, and machine learning hold promise for further advancements in lung cancer diagnosis and prognosis. AI applications for LCS are shown in Table 2.

The Road Ahead

Advancements in AI offer the potential to actualize harder tasks such as identifying image-based biomarkers and detecting lung nodules, which is another step towards personalized medicine. By enabling non-invasive and repeatable cancer detection, these innovations promise to enhance therapeutic management significantly.

To fully realize the benefits of AI in healthcare, there's a need for platforms that select various AI applications and integrate AI technology into medical systems. This integration is crucial for making AI a routine part of medical practice. There is also a need for future AI applications in LCS protocols to optimize the entire screening process (45, 46). This includes:

- Personalized risk assessment: Pre-screening AI applications will assess individual risk factors to optimize patient eligibility criteria.
- Low-dose imaging protocols: With deep learning-based algorithms, image selection will employ low-dose protocols to maintain high image quality while minimizing radiation exposure.
- Automated nodule detection: AI systems will automate the detection of lung nodules, reducing the workload on radiologists.
- Nodule characterization: Following detection, AI will aid in characterizing nodules as benign or malignant, optimizing resource utilization, and minimizing the likelihood of unnecessary biopsies or surgeries.

Table 2. Artificial intelligence applications for lung cancer screening

Function of the AI model	AI application
Reducing the radiation and true information extraction from the image	ClariCT.AI (ClariPI) (50)
Lung nodule detection (Computer-Aided Diagnostic Systems)	LIDC-IDRI (51, 52, 53)
	LUNA16 (51, 52, 53)
	ELCAP (51, 52, 53)
	ANODE09 (51, 52, 53)
Nodule detection and 3D visualization (Convolutional Neural Networks)	CMixNet (55)
	IR-UNet++ (45, 46, 56)
	MaskRCNN (57)
Nodule segmentation	UNet (59, 60)
	FCN (61, 62)
Virtual biopsy	CANARY (65)
Models designed for clinical outcomes	Perez-Morales et al. (67)
	Yu et al. (68)
	Cousin et al. (69)

FCN: Fully Convolutional Network

While the potential of AI in LCS is unlimited, several challenges be addressed to unearth its full benefits. Integration of AI algorithms into existing healthcare workflows requires careful validation, regulatory approval, and implementation strategies to ensure seamless adoption and compatibility with clinical practice. Also, the ethical and legal implications of AI in healthcare, including data privacy, transparency, and accountability, must demand careful consideration. Regulatory guidelines are essential to protect patient rights and ensure the responsible development of AI technologies in the medical field (46).

Collaboration between interdisciplinary teams of clinicians, data scientists, engineers, and policymakers is crucial to driving innovation into the real world. With partnerships between academia, industry, and healthcare institutions, AI's impact on LCS and beyond will be immense (70).

CONCLUSION

In summary, innovative technologies and analytical methods are transforming our approach to lung cancer management, offering new areas for early detection, personalized treatment, and improved patient outcomes. However, ongoing research and collaboration are crucial to maximizing the potential and addressing the potential risks of these groundbreaking advancements in clinical practice.

Ethics Committee Approval: *N/A*

Informed consent: N/A

Conflict of Interest: *One author of this article, Ateş Kutay Tenekeci, is a member of the editorial board of the Turkish Medical Student Journal. However, he did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.*

Author Contributions:

Concept: A.A.Ü., Design: A.A.Ü., Literature Search: A.A.Ü., Y.Y., G.S., A.K.T., Writing: A.A.Ü., Y.Y., G.S., A.K.T.,

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

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TMSJ
TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2024;11(2):40-9
DOI: 10.4274/tmsj.galenos.2024.2024-2-2

ORIGINAL ARTICLE

EVALUATION OF THE PERCEPTIONS AND ATTITUDES OF MEDICAL STUDENTS AGAINST THE COVID-19 PANDEMIC

Emir İskifoğlu[1], Ayşenaz Köşker[1], Elif Bulut[1], Mehmet İlker Beyaz[1], Pelin Durusoy[1], Yusuf Gül[1], Müge Kılıç[2], Gözde Kubat[3], Hayati Bilgiç[3], Meriç Yavuz Çolak[4], Selma Aydın[3], Fazıl Serdar Gürel[3]

[1]Başkent University School of Medicine, Ankara, TÜRKİYE
[2]Başkent University Kahramankazan Vocational School, Department of Management and Organization, Program of Business Administration, Ankara, TÜRKİYE
[3]Başkent University School of Medicine, Department of Medical Education, Ankara, TÜRKİYE
[4]Başkent University School of Medicine, Department of Biostatistics, Ankara, TÜRKİYE

ABSTRACT

Aims: The Coronavirus Disease of 2019 pandemic has negatively affected human life all over the world. The current study aims to evaluate the perceptions and attitudes of medical students regarding the pandemic while raising awareness about the pandemic's social, economic, psychological, and academic reflections.

Methods: The research data were obtained through a questionnaire administered to 371 medical students and literature reviews. The questionnaire was administered through Google Forms. While preparing the questionnaire, the Scale of Evaluation of Perceptions and Attitudes towards the Coronavirus Disease of 2019 outbreak was used.

Results: It was found that male students and smokers viewed the disease as more dangerous, while female students presented avoidance behaviors more commonly. Students in the pre-clinical years tended to attribute the pandemic to conspiratorial and environmental reasons more than students in the clinical years. Second- and fourth-year students had higher avoidance behaviors than first-year students. Students who experienced the disease had higher scores in perception sub-dimensions, while students whose relatives had Coronavirus Disease of 2019 were more prone to avoidance behaviors.

Conclusion: It was determined that the Coronavirus Disease of 2019 pandemic affected students' mental well-being negatively and that the students' perception of disease, cause, control, and avoidance behaviors differed according to factors such as gender, smoking status, grade, and experiencing the disease.

Keywords: Behavior, COVID-19, medical students, perception

INTRODUCTION

Since 2019, the coronavirus pandemic has had various effects on many areas of human life, ranging from limited social interactions to economic hardships. The Coronavirus Disease of 2019 (COVID-19), which caused more than one million deaths less than a year after it was first reported in Wuhan, China, may be considered one of humanity's biggest challenges in the 21st century. Many states and organizations conducted studies to prevent, treat, and control the disease from the first moments of the fight against the pandemic (1).

Classifying the outbreak as a pandemic is a significant declaration in terms of its global effects on economic and social fields as well as the field of health (2). Therefore, it is essential to understand the psychological and social effects of the

Address for Correspondence: Emir İskifoğlu, Başkent University School of Medicine, Ankara, TÜRKİYE
e-mail: emiriskifoglu@hotmail.com
ORCID iD of the authors: Eİ: 0009-0005-7002-2752; AK: 0009-0009-2396-9141;EB: 0009-0004-0863-2907; MİB: 0009-0001-6918-8035; PD: 0009-0009-9651-3874; YG: 0009-0004-9100-8258; MK: 0000-0003-1538-6738; GK: 0000-0002-0173-1054; HB: 0000-0001-5208-3053; MYÇ: 0000-0002-0294-6874; SA: 0000-0003-4231-3980; FSG: 0000-0002-6657-6147.
Received: 09.02.2024 Accepted: 29.05.2024

Cite this article as: İskifoğlu E, Köşker A, Bulut E et al. Evaluation of the perceptions and attitudes of medical students against the COVID-19 pandemic. Turk Med Stud J. 2024;11(2):40-9.

pandemic, first on society and then on the smaller groups that make up society. Measures taken on behalf of public health may affect social relations by weakening skills such as coping with stress, emotional control, and adaptation, which may lead to feelings of loneliness and fear being experienced more intensely. Along with factors such as quarantine, social isolation, and fear of illness, economic hardships may also advance psychological difficulties (3).

According to World Bank data, the crisis greatly affected global poverty, especially due to the disproportionate loss of income in the population working in the physical sectors that were more affected by the pandemic, which led to inequalities in society (4). Workers with lower education levels, women, and the younger side of the working population who were already disadvantaged have been affected more harshly (4). Türkiye's economy has also been exposed to the adverse effects of the pandemic (5). These outcomes and economic inequalities may have detrimental effects on university students since most of them are economically dependent on their families. Therefore, one of the groups most affected by the pandemic psychologically is university students (6, 7). Since emotional difficulties are one of the most common obstacles to academic success, it can be said that university students constitute a risk group (8). Emotional stress can affect the social and academic lives of students and reduce their success in higher education (9). Factors such as online education, staying away from class and campus life, and the anxiety of not having the necessary dominance over the profession they will perform in the future, in addition to other negative effects of the pandemic, have left students in a psychologically difficult situation (10).

Alsoghair et al. (11) found that 28.8% of fourth- and fifth-year medical students agreed that there was a higher chance of them being infected with COVID-19 than others. A study conducted on medical students in the United States found that most students (74.7%) agreed that the pandemic disrupted their education, and 83.4% accepted the risk of infection if they could return to the clinical setting (12). Furthermore, although online education may be sufficient to obtain information, it can create a feeling of inadequacy in medical students due to the lack of a physical environment for learning clinical skills (7).

The Coronavirus Disease of 2019 Pandemic

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or COVID-19 outbreak, which was first reported in Wuhan, China, in 2019 and then spread all over the world, was characterized as a pandemic by the World Health Organization (WHO) on March 11, 2020 (13). According to WHO data, as of January 14, 2024, the total number of cases reported was 774,291,287, and the total number of deaths was 7,019,704 (14).

Although most coronaviruses pathogenic to humans cause relatively mild clinical symptoms, there are exceptions, such as SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which are highly transmissible and pathogenic, not much different than COVID-19 (15, 16). After the SARS-CoV epidemic that emerged in China in 2002 and 2003, MERS-CoV was seen in the Middle East 10 years later, and finally, the SARS-CoV-2 pandemic in 2019, which infected more people than the previous coronavirus outbreaks (16).

The main transmission route of the COVID-19 virus is through the aerosol respiratory droplets of the infected individual, and the highest risk of transmission occurs as a result of close contact (approximately 2 meters) with the carrier individual (17, 18). Sneezing, coughing, and talking allow the airborne spread of the COVID-19 virus (18). In confined spaces with limited ventilation, the virus can remain suspended in the air for a longer period and spread over a longer range (17). In addition, transmission can also occur by touching the mucosal surfaces (mouth, nose, and eyes) after contact with contaminated objects (18). It is known that regular and meticulous washing of hands with antiseptic soap for at least 20 seconds (especially before eating or after sneezing or coughing) and disinfecting frequently used surfaces at regular intervals reduce the spread of the COVID-19 virus by physical conctact, which is one of the most important ways of transmission (19). Therefore, hands should be kept away from the face as much as possible. In addition, respiratory hygiene is just as important as the virus can spread through the air via respiratory droplets. Respiratory hygiene includes covering the mouth when sneezing or coughing and wearing a mask. During the pandemic, social distance rules should be followed in all areas, and crowded environments should be avoided (19).

To keep the COVID-19 pandemic under control in the long term, it was vital to produce effective vaccines and deliver them to the majority of the world's population, in addition to individual protection methods. Vaccine applications are important tools, even if they are not sufficient alone to prevent the pandemic. The efficiency of vaccines during the pandemic depends on multiple factors such as sample size, demographic factors, host factors, the type of vaccine, and the number of doses (20).

As of January 30th, 2024, according to the numbers shared by official government agencies, approximately 71% of the world population has received at least one dose of a SARS-CoV-2 vaccine, and 13.53 billion doses have been administered in total (21). In Türkiye, as of September 24th, 2023, in the population aged 18 and over, the rate of first-dose vaccination was 93.38%, the second-dose vaccination rate was 85.70%, and the third-dose vaccination rate was 45.5%, according to the Ministry of Health of the Republic of Türkiye (22). According to the mathematical model developed by Watson et al. (23), considering the official number of deaths, it has been estimated that 18.1 million people would have lost their lives if there were no vaccinations within one year and that existing vaccinations have prevented 79% of these estimated deaths.

Although it is not sufficient on its own, as stated before, vaccination is an important step in controlling the pandemic and restoring social and economic order as soon as possible. For this purpose, it is crucial to eliminate the prejudices in every society against vaccination or protection methods by raising

the necessary awareness. According to the report of the Center for Countering Digital Hate, the number of followers of social media accounts managed by so-called anti-vaccine movements has increased by at least 7.8 million in roughly the first year of the initial reporting of COVID-19, and this movement revealed an annual profit of approximately one billion United States dollars in social media (24). Authorities must focus on instilling confidence in those who have doubts and fears to prevent the negative consequences of anti-vaccination (25).

Perception and Attitudes

Fears associated with the disease, the need for constant protection, and practices such as social distancing and quarantine, which limit social relations, have also negatively affected social and individual psychology during the COVID-19 pandemic. As a result of these factors, extreme stress, anxiety, and depression have been observed (26).

In a study conducted by Quintiliani et al. (27) in Italy, it was shown that 54.4% of university students had decreased attention spans and 55% had concerns regarding exam outcomes. It was also found that 89.4% experienced increased stress (27). Another similar study conducted on university students in Spain found that 57.5% of the students felt worse psychologically, while 14.7% felt much worse after COVID-19 (28).

The COVID-19 pandemic has created social and psychological effects in Türkiye as well as all over the world. In a survey study conducted by Satici et al. (29) in 2021 investigating the psychological effects of the pandemic on society, it was found that fear of COVID-19 significantly increased depression, anxiety, and stress and decreased life satisfaction.

In another study conducted by Peker and Cengiz (30), the finding that fear of COVID-19 reduces happiness levels and increases stress is supported, and it has been reported that stress coping strategies reduce stress, and those who use these techniques have lower psychopathological risk levels when they encounter stress related to the pandemic.

Cam et al. (31) stated that in Türkiye, 64.6% of the university students showed signs of depression, 45.2% felt anxiety, 45.2% experienced stress, and 34.5% experienced post-traumatic stress disorder (PTSD) symptoms (all of which are students' self-diagnosis), and female gender and low-income family relationships are important risk factors for the ailments mentioned above. Torun and Torun (32) found that most medical students experienced severe anxiety about contracting the COVID-19 infection, and their stress levels increased, especially in females and students from low-income families, and one-third of them experienced disruptions in their sleep and eating patterns.

According to the findings of Oral and Karakurt (33), it was determined that university students' uncertainty and intolerance due to COVID-19 increased significantly. This increase may cause students to experience negative emotions more frequently or have difficulty adapting to daily life, thus perceiving unforeseen events as more dangerous, and may increase their tendency to experience high stress, anxiety, and depression (33).

Çınar Tanrıverdi et al. (34) reported that 76.3% of medical students preferred face-to-face education, 25.1% of these students experienced PTSD symptoms, and 23.6% had insomnia. It was found that PTSD symptoms were more common in students who followed the news about the pandemic on social media, and similar to previous studies, students were more concerned about the health of their relatives than their own (34). It has been reported that students in the more advanced academic years were more hopeless about the impact of the pandemic on their lives (35).

Therefore, it can be said that studies conducted on medical students in Türkiye have also yielded similar results to studies conducted on university students in different parts of the world mentioned previously.

It is important to raise awareness of the disease in society to control a potential outbreak in the future and take action on the effects of the recent COVID-19 pandemic. For this reason, a comprehensive understanding of perceptions and reactions against the disease is vital in combat strategies, and awareness of the potential effects and consequences of COVID-19 on the individual should be provided (36, 37). Raising public awareness will also encourage individual measures to prevent diseases (37).

This study aimed to evaluate and examine the perceptions and attitudes of medical students after the COVID-19 pandemic, raise awareness about the effects of the pandemic, such as depression, anxiety, health anxiety, and social isolation, along with the social, economic, and psychological reflections of the pandemic, and contribute to literature research.

MATERIAL AND METHODS

In this descriptive, cross-sectional study, all the rules specified in the "Higher Education Institutions Scientific Research and Publication Ethics Directive" were complied with and approved by the Başkent University Medical and Health Sciences Research Board (date: 01.02.2022, decision number: KA22/51). Informed consent was obtained from all of the participants.

Within the scope of the above-mentioned literature reviews and this research, it has been observed that different attitudes and behaviors toward the perception of COVID-19 disease were exhibited. Accordingly, the following hypotheses were formed:

H1: There is no significant difference in the perception of the disease by gender.

H2: There is no significant difference between the academic years of the students for the perception subscales (disease, cause, control) of the COVID-19 disease.

H3: There is no significant difference between the students who experienced the disease (themselves or through a relative) and those who had not, according to their avoidance behaviors.

H4: There is no significant difference between the disease perceptions of smoking and non-smoking students.

Statistical Analyses

Statistical analyses within the research scope were made using the IBM SPSS Statistics 25.0 package program. Descriptive statistics of the variables are given as frequency and percentage for discrete data, while mean and standard deviation are given for continuous data. The Kolmogorov-Smirnov test was used to control the study's normality distribution and it was detected that the data was normally distributed. Correlation analysis was applied when checking the relationship between categorical variables. Independent Sample t-test and analysis of variance test were used in statistical analysis for the study data with normal distribution. The groups that made the difference in the variables whose significance was detected with least significant difference from post hoc tests were determined. The hypotheses were evaluated by comparing p-values obtained in the statistical analyses and $p<0.05$ was considered as statistically significant.

Sample

The sample of this research consists of 371 students studying at the Başkent University School of Medicine in Ankara in the 2021-2022 academic year. 68% of the students were female and 32% were male. It was observed that most of the participants were first-year students with 22%, and third- and fourth-year students followed with 20%. The gender distribution of the students according to year levels is given in Table 1. As can be seen in Table 1, the participants are mostly female in all academic years. The distribution of COVID-19 transmission status according to the academic years of the students is given in Table 2. Although 55% of sixth-year students have had COVID-19, the majority of other-year students have not. It was determined that most of the students included in the study had relatives who had COVID-19.

Measurement Tools

Perceptions and Attitudes towards the COVID-19 Pandemic Questionnaire were used in the study. The questionnaire is a 5-point Likert questionnaire and consists of a total of fifty-three items (38). The forms were created by Çırakoğlu (38) during the swine flu (H1N1) epidemic. Then, it was adapted to be used in the COVID-19 pandemic and the validity and reliability of the forms were verified by Artan et al. (39). With the context given, the questionnaire consisted of four subscales later adapted for the COVID-19 pandemic: perception of the disease, perception of causes of the disease, perception of control of the disease, and avoidance behaviors (38, 39). Perception subscales (perception of disease, causes, and control) are 5-point Likert-type questionnaires consisting of options between "1- Strongly agree" and "5- Strongly disagree." Options in the avoidance behaviors subscale varied from "1- I never did this" to "5- I frequently did this," some of which were reverse coded (38, 39).

Table 1. Gender distribution of students according to grade levels.

	Gender	
	Female (n=253)	**Male (n=118)**
Grade 1	58 (72.5%)	22 (27.5%)
Grade 2	47 (69.1%)	21 (30.9%)
Grade 3	48 (65.8%)	25 (34.2%)
Grade 4	49 (66.2%)	25 (33.8%)
Grade 5	38 (67.9%)	18 (32.1%)
Grade 6	13 (65%)	7 (35%)
Total	253 (68.2%)	118 (31.8%)

Perception of Disease

The subscale consisting of 8 items for the perception of disease measures the perception of the disease's properties, such as contagiousness and mortality. Higher scores in this subscale were accepted as the participants viewed the disease as more dangerous than participants with lower scores.

Perception of Cause

The subscale consists of 18 items for the perception of causes, including items questioning the perceptions of the reasons for the existence of the disease. Items in this subscale were intended to question three different concepts that may have been believed to have caused the pandemic, including conspiracy (questions 9-14), environment (questions 15-22), and faith (questions 23-26). The conspiracy subgroup evaluates the prevalence of beliefs such as an organization or a government knowingly causing the pandemic with ulterior motives such as experimenting on a biological weapon or a way of creating more demand for medicine to contribute to the economic system. The environment subgroup questions environmental reasons such as pollution, global warming, unhealthy diet, and overpopulation. The faith subgroup aims to determine if the participant attributes the pandemic to a religious reason such as god's wrath against social degradation or the pandemic being predetermined in humankind's destiny. These subgroups together form the perception of cause subscale and were compared together with other subscales as a whole while the faith, environment, and conspiracy subgroups were compared between themselves separately.

Table 2. Distribution of students who have had COVID-19 and relatives of the students who have had COVID-19 according to their grade levels.

	Had COVID-19		Relatives had COVID-19	
	Yes (n=149)	**No (n=222)**	**Yes (n=312)**	**No (n=59)**
Grade 1	32 (40%)	48 (60%)	66 (82.5%)	14 (17.5%)
Grade 2	33 (48.5%)	35 (51.5%)	62 (91.2%)	6 (8.8%)
Grade 3	33 (45.2%)	40 (54.8%)	60 (82.2%)	13 (17.8%)
Grade 4	15 (20.3%)	59 (79.7%)	59 (79.7%)	15 (20.3%)
Grade 5	25 (44.6%)	31 (55.4%)	49 (87.5%)	7 (12.5%)
Grade 6	11 (55%)	9 (45%)	16 (80%)	4 (20%)
Total	149 (40.2%)	222 (59.8%)	312 (84.1%)	59 (15.9%)

COVID-19: Coronavirus Disease of 2019

Perception of Control

The subscale for the perception of control consists of 13 items in total, and it aims to evaluate the reliability of both personal and mandated prevention techniques in the eyes of the participants, including items such as "What is done to stop the spread of the disease is sufficient" and "The personal measures I take are sufficient to avoid catching this disease".

Avoidance Behaviors

The avoidance behaviors subscale consists of 14 items. It aimed to evaluate the prevalence of avoiding the disease mentally by including items such as "not reading newspaper news about the pandemic" and "leaving places where the pandemic is discussed". Participants with higher scores in the avoidance behaviors sub-dimension tend to avoid talking, reading, and listening about the disease, presumably as a way of avoiding stress and negative thoughts that may manifest. Avoidance behaviors are a highly prevalent symptom and a major factor in maintaining anxiety (40).

RESULTS

In this study, the perception (of illness, control, and cause) and avoidance behaviors subscales were used to measure the perceptions and attitudes of students who received medical education in the 2021-2022 academic year toward the COVID-19 pandemic. The reliability of the scales was 84.7% and 83.9%, respectively.

When the smoking status of the participants was evaluated, it was concluded that the sixth-year students smoked the most at 30%, and the relevant distributions are given in Table 3. The perceptions and avoidance behaviors scores of the participants according to smoking status, gender, and whether they or a relative had COVID-19 are given in Table 4. While there was no significant difference in perception of cause (p=0.18) and avoidance behaviors (p=0.832), it was concluded that the perception of disease (p=0.006) and the perception of control (p=0.023), which are the subscales, differ between smokers and non-smokers. With the findings obtained, it was concluded that the perception of the disease and control was higher in smokers, and hypothesis H4, "There is no significant difference between the disease perception of smoking and non-smoking students", was rejected.

According to Table 4, in the comparison between individuals who have had COVID-19 and individuals who have not, there was no difference between avoidance behaviors (p=0.778), but a statistically significant difference was found between perception scores. It was concluded that the sub-dimensions of the perception of illness (p<0.001), the perception of cause (p=0.019), and the perception of control (p=0.021) were higher in those who had COVID-19. It is seen that students who had COVID-19 had a higher tendency to attribute the pandemic to an alternative reason, with the highest mean scores being in the conspiracy subgroup (Table 5). A statistically significant difference was found in the avoidance behaviors of individuals whose relatives had COVID-19 and those whose did not (p=0.035) while there was no difference in the perception of the disease (p=0.198), perception of cause (p=0.393), and perception of control (p=0.785) subscales. It was concluded that the students with a relative who had COVID-19 had higher scores in avoidance behaviors. With these findings, hypothesis H3, "There is no significant difference between the students who experienced the disease (themselves or through a relative) and those who did not according to their avoidance behaviors", was rejected.

When the statistical analysis results were evaluated, the perception of disease (p=0.015) and avoidance behaviors (p=0.048) showed statistically significant differences according

Table 3. Smoking status according to academic grades.

	Smoking status	
	Smoker (n=69)	Non-smoker (n=302)
Grade 1	12 (15%)	68 (85%)
Grade 2	10 (14.7%)	58 (85.3%)
Grade 3	12 (16.4%)	61 (83.6%)
Grade 4	15 (20.3%)	59 (79.7%)
Grade 5	14 (25%)	42 (75%)
Grade 6	6 (30%)	14 (70%)
Total	69 (18.6%)	302 (81.4%)

Table 4. Scale score comparisons according to students' demographic characteristics.

		Perception of disease		Perception of cause		Perception of control		Avoidance behaviors	
		Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Gender	Female	3.20±0.45	0.015*	2.24±0.67	0.146	2.66±0.51	0.056	3.17±0.73	0.048*
	Male	3.32±0.45		2.13±0.64		2.77±0.57		3.00±0.84	
Had COVID-19	Yes	3.36±0.48	<0.001*	2.30±0.70	0.019*	2.77±0.56	0.021*	3.13±0.77	0.778
	No	3.16±0.41		2.14±0.63		2.64±0.50		3.10±0.77	
Smoker	Yes	3.37±0.47	0.006*	2.30±0.76	0.18	2.82±0.61	0.023*	3.09±0.83	0.832
	No	3.21±0.44		2.18±0.64		2.66±0.51		3.12±0.75	
Relatives had COVID-19	Yes	3.25±0.44	0.198	2.22±0.66	0.393	2.70±0.54	0.785	3.15±0.75	0.035*
	No	3.17±0.49		2.14±0.69		2.68±0.50		2.92±0.81	

Independent sample t-test, *p<0.05.
SD: Standard deviation, COVID-19: Coronavirus Disease of 2019

to gender. At the same time, there was no significant difference in the perception of causes (p=0.146) and the perception of control (p=0.056) subscales. It was concluded that although women's perception of illness was lower than men's, their avoidance behavior scores were higher. Considering this information, hypothesis H1, "There is no significant difference in the perception of the disease by gender", was rejected.

The comparison results of perception and attitude scores according to grades are given in Table 6. While it was statistically obtained that the scores of perception of disease (p=0.322) and perception of control (p=0.495) did not differ according to year levels. It was concluded that perception of cause (p<0.001) and avoidance behaviors (p=0.034) differed according to year levels. For the perception of cause subscale, post hoc analysis revealed a significant difference between the students in the pre-clinical and clinical years. The pre-clinical students (years 1, 2, and 3) had higher scores in the perception of the cause than the clinical students (years 4, 5, and 6) (p<0.001). The conspiracy, environment, and faith subgroups' mean scores are given in Table 7. According to the data obtained, first-, third-, and fifth-year students had higher scores in the conspiracy subgroup, and second-, fourth-, and sixth-year students' scores were higher in the environment subgroup. A significant difference was found in the avoidance behaviors subscale (p=0.034) according to grade levels. Post hoc analysis revealed that first-year students and second- and fourth-year students had significantly different scores in avoidance behaviors, and it was concluded that avoidance behaviors were more prevalent in second- and fourth-year students than first-year students. In light of this information obtained, hypothesis H2, "There is no significant difference between the academic years of the students for the perception subscales (disease, cause, control) of the COVID-19 disease", was rejected.

Table 5. Perception of cause sub-groups' comparison according to COVID-19 status.

		Conspiracy	Environment	Faith
		Mean ± SD	Mean ± SD	Mean ± SD
Had COVID-19	Yes	2.42±1.04	2.30±0.80	2.10±0.68
	No	2.12±0.84	2.24±0.76	1.98±0.67

SD: Standard deviation, COVID-19: The Coronavirus Disease of 2019

DISCUSSION

When the statistical analysis results were evaluated, the perception of disease (p=0.015) and avoidance behaviors (p=0.048) showed statistically significant differences according to gender. Although women's perception of disease was lower than men's, their avoidance behaviors were higher. It was concluded that male students perceived the disease as more dangerous than female students and that female students tended to avoid mediums and places where the disease is discussed more often. In a study conducted in the United

Table 6. Scale score comparisons according to students' grade levels.

	Perception of disease		Perception of cause		Perception of control		Avoidance behaviours	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Grade 1	3.30±0.43	0.322	2.42±0.67	<0.001*	2.73±0.62	0.495	2.91±0.71	0.034*
Grade 2	3.14±0.41		2.29±0.64		2.68±0.47		3.16±0.78	
Grade 3	3.25±0.54		2.31±0.74		2.76±0.64		3.12±0.80	
Grade 4	3.25±0.41		2.07±0.54		2.67±0.44		3.32±0.63	
Grade 5	3.27±0.40		1.97±0.63		2.66±0.40		3.10±0.86	
Grade 6	3.17±0.52		1.81±0.49		2.51±0.55		2.97±0.86	
Groups with significant difference			Grades 1, 2, 3 and, Grades 4, 5, 6				Grade 1 and, Grades 2, 4	

One-way ANOVA test, *p<0.05.
SD: Standard deviation

Table 7. Perception of cause sub-groups' comparison according to students' grades.

	Conspiracy	Environment	Faith
	Mean ± SD	Mean ± SD	Mean ± SD
Grade 1	2.54±0.91	2.43±0.81	2.17±0.84
Grade 2	2.36±0.93	2.37±0.71	1.98±0.68
Grade 3	2.40±1.01	2.32±0.87	2.16±0.70
Grade 4	1.93±0.78	2.23±0.70	2.00±0.53
Grade 5	2.03±0.93	1.98±0.70	1.92±0.48
Grade 6	1.80±0.78	1.96±0.65	1.59±0.50

SD: Standard deviation

States of America (USA), Wang et al. (26) observed that approximately 48% of the students experienced moderate-to-severe depression levels and approximately 38% experienced moderate-to-severe anxiety due to the COVID-19 pandemic. They found significant differences between genders in both parameters: females experienced both higher depression levels and anxiety (26). Some existing literature revealed female gender is associated with greater rates of anxiety, stress, and risk perception, while some studies found no correlation between gender and anxiety (41-43). Rana et al. (44) found that women had significantly more fear and worries about getting infected. In a study conducted on university students, Rodriguez-Besteiro et al. (45) also found that female gender was correlated with elevated risk perceptions. In conclusion, the current study contrasted similar studies on risk perceptions since statistical analysis found the feeling of danger to be higher in males. However, the statistical finding that female students practicing avoidance behaviors more prevalently may be related to females having higher anxiety, and stress (according to literature search) associated with COVID-19 (26, 31, 40-42).

A significant difference was not found between genders in the perception of control subscale (p=0.056) which meant that both genders had similar rates of trust in preventive measures. Contrasting the current study, regarding adherence and agreement to COVID-19 preventive measures according to gender, Galasso et al. (46) studied on 8 different countries with a total of 21,649 respondents in a two-wave survey in March and April 2020. The surveys revealed that agreement to preventive measures was higher in women in the first wave (46). In the second wave, agreement decreased among both females and males but the difference between genders persisted. The study also found a similar difference between genders in compliance with preventive measures, being higher in females (46). similarly, Rana et al. (44) found that women had more trust in government actions and measures regarding the pandemic and Ferrín et al. (47) found that females were more trusting of the efficiency of measures taken to avoid infection although they perceived the disease riskier than men.

While there was no difference in avoidance behaviors in the comparison between individuals who had COVID-19 and those who did not (p=0.778), a statistically significant difference was found between perception scores. It was concluded that the subscales, perception of illness (p<0.001), perception of causes (p=0.019), and perception of control (p=0.021) were all higher in those who had COVID-19. Therefore, students who had COVID-19 at some point viewed the disease as more dangerous and thought there could have been an alternative reason for the disease rather than traditional views, although they had higher trust in personal and mandated and prevention techniques' reliability. Cipolletta et al. (48) states that high-risk perception encourages preventive behaviors, which correlates with the finding that students who had COVID-19 perceive the disease to be more dangerous while they have more trust in preventive measures. Further analysis revealed that participants who had the disease believed in conspiratorial reasons more prevalently (Table 7). Zhang et al. (49) found increased rates of depression related to the pandemic in patients who had COVID-19. Therefore, higher scores in perception of the disease, which means a higher perception of danger, could potentially be related to higher anxiety, stress, and depression. In a study conducted in Türkiye by Fenercioglu et al. (50), it was found that 50.1% of the population had beliefs of conspiracy about the COVID-19 pandemic. However, a correlation between conspiratorial beliefs and past COVID-19 infection was not detected, while the current study found a significant difference in the perception of causes related to COVID-19 infection (50). Regarding the finding of a higher perception of control in students who have had COVID-19, Wong et al. (51) found that higher anxiety was associated with increased use of preventive measures, Ahorsu et al. (52) found an indirect association between health status and preventive behaviors via fear of COVID-19, and Taghrir et al. (53) found that as preventive behaviors increased, the risk perception declined in medical students in Iran. Considering health and fear of how dangerous a disease can be are driving factors to adherence to preventive measures, the findings are consistent with existing literature, and it can be concluded that having COVID-19 at some point causes feeling of danger regarding the disease to be higher and therefore elevates the rates of agreement to preventive measures.

Contrasting personally experiencing COVID-19 infection, relatives having COVID-19 were not found to be significant in perception sub-scales but were a significant factor in avoidance behaviors. A statistically significant difference was found in the avoidance behaviors of participants whose relatives had COVID-19 (p=0.035). Analysis revealed a higher rate of avoidance behaviors in participants who had a relative with COVID-19. Lee et al. (54) found that 20% of the students who participated in the study worried about their loved ones regarding the pandemic, while 31.8% of the students said the need to take care of their family affected their current and future plans. Tee et al. (41) found that female gender, being a student, and concerns for family were significantly associated with greater rates of anxiety and stress regarding the COVID-19 pandemic. Cao et al. (43) found gender not to be significant in anxiety, while having a relative or acquaintance infected with COVID-19 was related to higher anxiety. In another study, it was also found that medical students who had a relative infected with COVID-19 had higher positive responses to preventive practices (55). These findings correlate with higher avoidance behaviors in students with infected relatives since avoidance behaviors are a direct symptom of anxiety and literature search suggests that having a loved one diagnosed with COVID-19 increases anxiety (40, 41, 43). Avoidance behaviors could be an attempt to dam negative thoughts and not increase stress while dealing with the anxiety of having a loved one affected. Considering the finding that self-COVID-19 infection was not found to be significant in avoidance behaviors while avoidance behaviors were positively correlated with having a loved one with COVID-19 infection further supports the notion that people were generally more

worried about their loved ones rather than themselves during the pandemic. In conclusion, while personally experiencing COVID-19 infection caused the feeling of danger to be higher and, encouraged people to practice preventive techniques, having a relative infected with COVID-19 did not. Still, it rather pushed people to have avoidance behaviors presumably as an effect of anxiety.

It was found that the perception of disease (p=0.006) and the perception of control (p=0.023) differ between smokers and non-smokers. It was concluded that both scores of smokers were higher, meaning that smokers perceived the disease to be more dangerous than non-smokers and that they had higher trust in personal and mandated preventive measures. In a study done on adults residing in Jordan, Nusair et al. (42) found that female gender and being a smoker were correlated with elevated risk perception scores. White et al. (56) found that in the United States, most smokers (63.7%) believed that they had a higher risk regarding COVID-19, while Nyman et al. (57) stated that in the United States, 43.6% of smokers felt that smoking could increase the severity of COVID-19. In Hong Kong, Li et al. (58) found that the overall prevalence of high perceived susceptibility to and severity of COVID-19 in relation to smoking was 23.9% and 41.7%, respectively. Therefore, the finding of a higher perception of disease in smokers in the current study is supported by several similar studies, and it correlates with higher trust and potential adherence to preventive measures.

It was found that pre-clinical students' scores were higher than clinical students' scores in the perception of causes subscale (p<0.001), meaning that pre-clinical students were more inclined to believe alternative theories when it comes to what caused the pandemic. This difference may stem from clinical students' more advanced knowledge of the field of medicine, causing them to be more skeptical of unconfirmed information, although it is not possible to say certainly considering it is out of the scope of the current questionnaire.

It was found that second- and fourth-year students' avoidance behaviors were significantly higher than first-year students' (p=0.034). Higher scores of avoidance behaviors in second- and fourth-year students could be explained by the literature finding that upper-grade students experience more anxiety and hopelessness regarding the pandemic but this finding causes some uncertainty since there were no significant difference detected between first-, third-, fifth- and sixth-year students (35).

No significant difference was found between grades regarding the perception of disease (p=0.322) and the perception of control (p=0.495) sub-scales. There was no correlation between grade levels and feelings of danger or trust in preventive measures.

Considering the findings obtained and mentioned above, it has been determined that COVID-19 affects students in terms of social isolation and anxiety. In addition, it is seen that it negatively affects students' social and educational lives. It is predicted that the COVID-19 pandemic, which affects human life in psycho-social terms worldwide, will also affect the students' academic lives. For example, in a study conducted in the USA during the pandemic, it was stated that social isolation and economic uncertainty lead to mental difficulties such as loneliness, anxiety, and depression, and it was observed that the psychological resilience of individuals forming society decreased significantly compared to normal conditions (59). Another study conducted on medical students in the United States found that 67.5% of the participant students pointed out that they were exposed to increased depression, and 73% of them were exposed to increased feelings of anxiety (60). It was also found that 81% of medical students thought they had less control over their medical skills, and 70.9% thought that they were less competent in medical fields than previous medical students who did not go through a pandemic during their education (60). It has been reported that 70% of the students think that their general education quality has decreased due to the measures regarding the pandemic, and a significant number of students think that their clinical experience is insufficient (60).

This study has limitations in conducting the research with sample and cross-sectional data. These limitations should be considered when evaluating the results.

CONCLUSION

The statistical analysis results revealed the different perceptions and attitudes of medical students, which are important to grasp the aftermath of the COVID-19 pandemic fully. The results were compared with existing literature to further investigate the reasons behind certain perceptions and attitudes, which are vital to understanding psychological and social reflections of the recent COVID-19 pandemic and a potential future pandemic. This study may also contribute to future studies.

Ethics Committee Approval: *This study was approved by Başkent University Institutional Review Board (date: 01.02.2022, decision number: KA22/51).*

Informed Consent: *Informed consent was obtained from all of the participants.*

Conflict of Interest: *One author of this article, Emir İskifoğlu, is a member of the editorial board of the Turkish Medical Student Journal. However, he did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.*

Author Contributions: *Concept: E.İ., A.K., E.B., M.İ.B., P.D., Y.G., H.B., S.A., F.S.G, Design: E.İ., M.K., G.K., H.B., M.Y.Ç., S.A., F.S.G, Data Collection or Processing: E.İ., A.K., E.B., M.İ.B., P.D., Y.G., Analysis or Interpretation: E.İ., M.K., G.K., M.Y.Ç., Literature Search: E.İ., A.K., E.B., M.İ.B., P.D., Y.G., M.K., G.K., Writing: E.İ., A.K., E.B., M.İ.B., P.D., Y.G., M.K., G.K., H.B.*

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

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TMSJ
TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2024;11(2):50-4
DOI: 10.4274/tmsj.galenos.2024.2024-2-1

CASE REPORT

REPURPOSING EMPAGLIFLOZIN TO TREAT NEUTROPENIA IN A TURKISH GIRL WITH GLYCOGEN STORAGE DISEASE TYPE 1B

Hasan Selçuk Özkan[1], Ece Derin Aydın[1], Sakina Mammadova[1,2], Mahmut Çoker[1,2]

[1]Ege University School of Medicine, İzmir, TÜRKİYE

[2]Ege University School of Medicine, Department of Pediatrics, Division of Pediatric Inborn Metabolic Disorders and Nutrition, İzmir, TÜRKİYE

ABSTRACT

Recurrent infections in children are alarming symptoms that require further investigation, particularly for various immunodeficiency syndromes. However, concomitant physical examination and laboratory findings, along with detailed investigations on the nature of these infections, might be useful to identify further pathologies, such as neutropenia, which might be the underlying reason behind recurrent infections. In this case report, we aimed to provide a different perspective on recurrent infections in childhood and to highlight the importance of accompanying physical examination findings and careful history-taking. In addition, by using glycogen storage disease type 1b as a model disease, we aim to raise awareness of inborn errors of metabolism as possible differential diagnoses and to prove that through certain therapeutic measures such as drug repurposing, these diseases can be controlled, possibly leading to decreased morbidity and mortality in this patient group, which was once thought to have a devastating prognosis.

Keywords: Glycogen storage disease, hepatomegaly, immunodeficiency, inborn errors of metabolism

INTRODUCTION

Recurrent infections in children are important, as they might be the sign of various disorders, which include benign and temporary to malignant and life-threatening causes (1). Although both the locations of infections and their causative agents can provide valuable information regarding the underlying cause of these recurrent infections, due to this variety and the many unknown conditions yet to be identified, the differential diagnosis of recurrent infections remains a significant challenge (1).

In this case report, we present glycogen storage disease type 1b (GSD1b) as a cause of neutropenia, presenting with recurrent infections in a 6-year-old Turkish girl born to consanguineous parents, who additionally presented with repeating attacks of hypoglycemia and metabolic acidosis, coupled with massive hepatomegaly.

CASE REPORT

Our patient is a 6-year-old female who was diagnosed with GSD1b at the age of 4 months. She was born to third-degree consanguineous parents at term, breastfed for 2 months, and has been under the care of the division of pediatric inborn metabolic disorders and nutrition at the Ege University Faculty of Medicine Children's Hospital since 2019. Her first clinical investigations leading to her diagnosis were initiated after the onset of fever attacks, which was the first symptom observed at the age of two months. Genetic analysis conducted in 2017 revealed a homozygous c.406T16>A mutation in the *SLC37A4* gene, consistent with GSD1b. The patient remained under follow-up at another tertiary care center until 2019.

During her first examination in our center in 2019, the patient had developmental delays, including late speech acquisition and short stature, with her current body weight and height

Address for Correspondence: Hasan Selçuk Özkan, Ege University School of Medicine, İzmir, TÜRKİYE
e-mail: hselcukozkan@gmail.com
ORCID iD of the authors: HSÖ: 0000-0001-5282-6179; EDA: 0009-0004-1874-5622; SM: 0000-0001-8082-0567; MÇ: 0000-0002-6308-6804
Received: 01.02.2024 Accepted: 06.05.2024

Cite this article as: Özkan HS, Aydın ED, Mammadova S et al. Repurposing empagliflozin to treat neutropenia in a Turkish girl with glycogen storage disease type 1b. Turk Med Stud J. 2024;11(2):50-4.

being -1.76 standard deviation score (SDS) and -3.34 SDS, respectively. Dysmorphological findings such as frontal bossing, hypertelorism, epicanthus, flat nasal bridge, and thin lips were present. The detailed endocrinological investigations were not significant in the patient whose skeletal age was compatible with her calendar age.

Her detailed medical history revealed recurrent infections and fevers since she was two months old, which led to frequent hospitalizations in the last six years. Subsequently, the patient has had a total of 8 hospitalizations in our center since birth due to infection-related episodes of acidosis and hypoglycemia. The most recent hospitalization in January 2024 at our center was prompted by elevated lactate levels, incidentally discovered during a routine outpatient follow-up period.

The patient's initial presentation in our center in 2019 occurred due to acute respiratory distress and a 2-3-day history of persistent cough, complicated by a metabolic decompensation that could not be controlled by the first care providers. The patient had a blood glucose level of 32 mg/dL, a pH of 7.06, and a serum bicarbonate (HCO_3-) level of 7.5 mmol/L with a lactate level of 21 mmol/L, suggestive of severe hypoglycemia and severe metabolic acidosis. Following the first physical examination, no pathological findings were observed except for massive hepatomegaly, with the liver being palpable in the right upper quadrant. Her triglyceride levels also exceeded >250 mg/dL in repeated measurements during our follow-up for years.

A detailed inquiry into past medical history revealed recurrent skin abscesses, two episodes of gastroenteritis, and persisting painful oral ulcers, raising suspicion of autoimmune, autoinflammatory, or rheumatological conditions and various errors of immunity. Measurement of immunoglobulin (Ig) levels revealed normal levels of IgA, IgG, and IgM. The ratio of the cluster of differentiation 3 positive T cells was minimally low at 55.2% (normal range: 57-85%), which prompted assessment for Ebstein-Barr virus (EBV), which came positive with EBV deoxyribonucleic acid (DNA) at 1370 copies/mL. Other laboratory examinations, including direct Coombs, antinuclear antibodies, and cytomegalovirus DNA, were negative. A burst test was conducted to exclude neutrophil function disorders, which came normal; however, her neutrophil counts were repeatedly under $1.5x10^3$, suggestive of consistent neutropenia.

An initial abdominal X-ray revealed hepatomegaly. A Doppler ultrasound examination of the portal vein, performed to reveal the etiology of her massive hepatomegaly, was reported to be normal. However, a consequent abdomen magnetic resonance imaging (MRI) showed a craniocaudal liver length of 151 mm (normal range: <109 mm, adjusted for age and sex) by physical examination findings. Additionally, a grade 2 hepatosteatosis was detected. Abdominal X-ray and MRI findings can be found in Figure 1.

The patient's general condition improved with the administration of necessary antibiotics and supportive therapy. The patient was discharged with a treatment plan that included the following: oil containing medium-chain triglycerides to manage her hypertriglyceridemia, regular raw starch to be mixed with either water or soy milk before consumption, and a dietary plan to prevent further hypoglycemia attacks, consisting of regular feeding periods with four-hour intervals. Additionally, she was prescribed allopurinol for her accompanying hyperuricemia, along with vitamin D and calcium supplements.

During her follow-up appointments in the following years, similar complaints, including recurrent infections, were present and occasionally led to hospitalizations, which are summarized in Figure 2. Her persistent neutropenia preceding

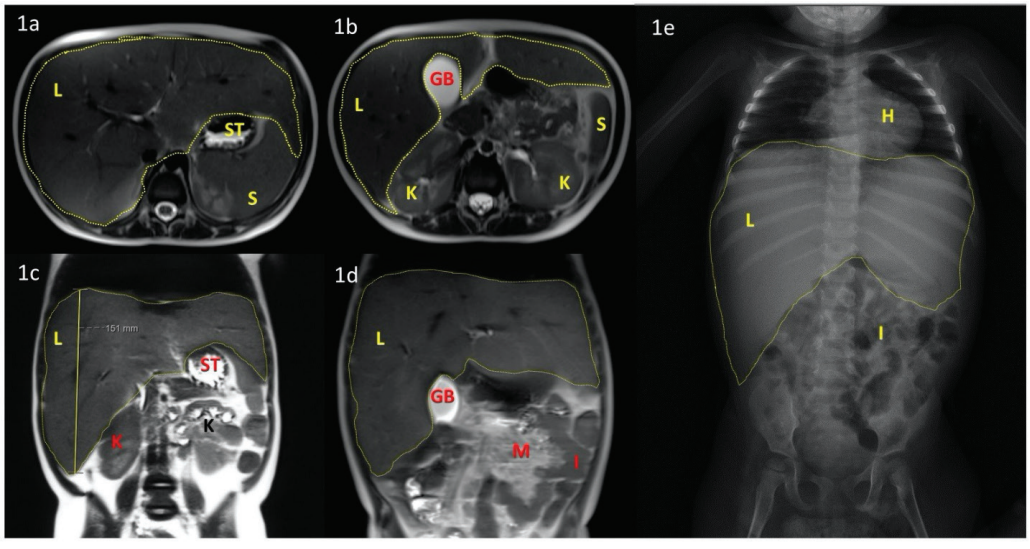

Figure 1: Abdominal MRI and X-ray findings of the patient. a and b) Sagittal upper abdominal T2-weighted MRI slices show massive hepatomegaly, which is occupying both upper quadrants and crossing the midline. c and d) Coronal upper abdominal slices of the same findings, with the liver craniocaudal length reaching 151 mm. e) Abdominal X-ray showed massive hepatomegaly, occupying most of the upper quadrants.
L: Liver, ST: Stomach, S: Spleen, K: Kidney, GB: Gallbladder, I: Intestines, M: Mesentery, H: Heart, MRI: Magnetic resonance imaging

these infections required regular treatment with filgrastim, a recombinant granulocyte-colony stimulating factor (G-CSF), which requires administration of infusions and a subsequent hospital stay or repeated subcutaneous injections. The G-CSF therapy was started as the first decision during her hospital stay between 03.07.2020-01.08.2020. A summary of the evolution of her laboratory results can be seen in Figure 3. After the publication of promising studies on the role of empagliflozin in these patients for the treatment of neutropenia in 2021, a treatment plan with oral empagliflozin has been conceptualized and applied for our patient to wean her off regular G-CSF treatments, as this patient will require lifelong treatment (2). G-CSF therapy was stopped during her hospital stay between 07.07.2021-03.08.2021 and empagliflozin treatment was started at 09.07.2021. Empagliflozin is preferred as it may also alleviate inflammatory bowel disease (IBD) symptoms in this high-risk patient group (3). The positive effects of empagliflozin on leukocyte and neutrophil counts can be found in Figure 4.

DISCUSSION

Glycogen storage disease type 1 is an autosomal recessive disease, also known as von Gierke's disease. Both forms of GSD type 1, namely 1a and 1b, are characterized by a tendency to develop recurrent hypoglycemia with rapidly and significantly elevated lactate levels, and the presence of hypoketotic hypoglycemia is typical and of utmost diagnostic relevance (4).

In GSD1b, the defective enzyme is glucose-6-phosphate translocase within the membrane of the endoplasmic reticulum and is active in the terminal stages of glycogenolysis and gluconeogenesis (4). Glucose-6-phosphate translocase transports substrates across the endoplasmic reticulum,

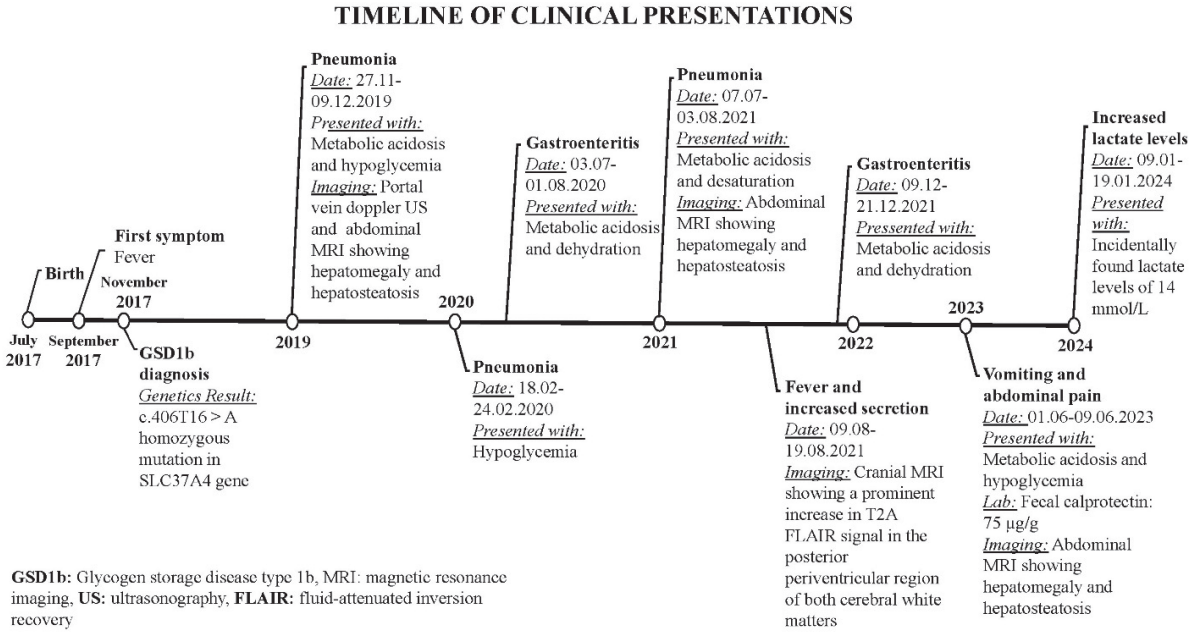

Figure 2: Timeline schema representing the hospital presentations due to underlying infectious diseases.

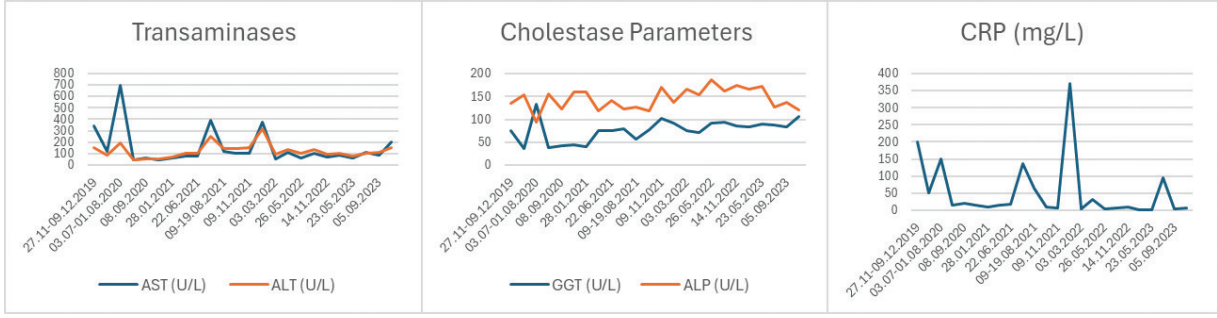

Figure 3: Laboratory parameters throughout the disease, only the highest results from every hospitalization period, and every result from outpatient care are shown. Normal value ranges are AST: <31 U/L, ALT: <34 U/L, GGT: <38 U/L, ALP: 142-335 U/L, and CRP: 0-5 mg/L. The time intervals marked with hyphens represent multi-day inpatient treatments where many measurements took place, and among these, the greatest values have been included in the figure.
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, CRP: C-reactive protein

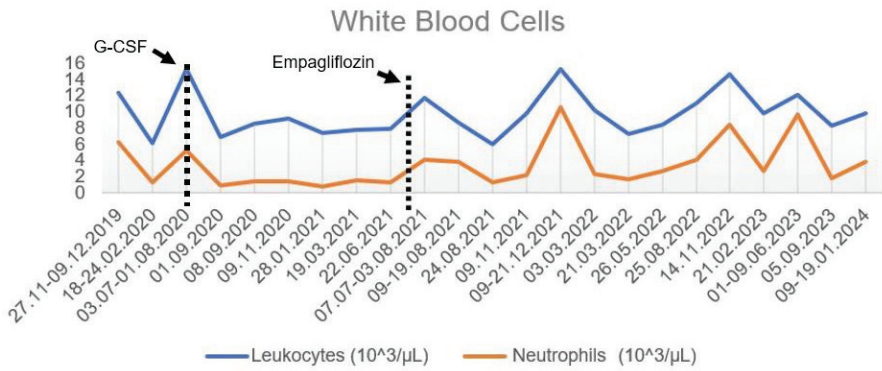

Figure 4: Effect of G-CSF and empagliflozin on leukocyte and neutrophil counts. The peaks are consistent with recurrent infections. The time intervals marked with hyphens represent multi-day inpatient treatments where many measurements took place, and among these, the greatest values have been included in the figure.
G-CSF: Granulocyte-colony stimulating factor

eventually releasing the free glucose into circulation (5). This enzyme can be found in many tissues and organs, such as the kidneys, small intestine, pancreatic islets, and in especially high concentrations in the liver (6). Typical findings, therefore, include hepatomegaly, growth retardation due to a deficiency of growth hormone, hypoglycemia, hyperuricemia, and hyperlipidemia (7, 8). The pathophysiology behind these symptoms is straightforward, while the problem lies in where the glycogen is stored and its toxic accumulation (4). All of which are present in our case as well.

Neutropenia and IBD mimicking autoimmune conditions are, on the other hand, specific for GSD1b (4). There are different hypotheses to explain the reason for increased autoimmunity in GSD1b patients, such as dysfunction of neutrophils and repetitive immunologic activation because of the immunological defect in the exclusion of microbial antigens (9).

Glycogen storage disease 1b patients are more likely to present with autoimmune conditions of the thyroid gland, myasthenia gravis, and IBDs like Crohn's (9). In our patient, a single measurement of fecal calprotectin during an infection-free period was 75 µg/mg (normal range <50 µg/mg), which might constitute an indication for colonoscopy, but only if the patient becomes symptomatic for IBD.

Although, literature data also highlight impaired activation of some immune pathways, neutropenia and impaired neutrophil function have been long believed to occur in GSD1b patients, mainly due to the accumulation of a toxic metabolic called 1,5-anhydroglucitol-6-phosphate (1,5AG6P) in the neutrophils and presented as 1,5-anhydroglucitol (1,5AG) as a nondegradable glucose analog in plasma, because of the deficiency of transporting protein glucose-6-phosphate transporter in neutrophils leading to a decrease in dephosphorylation of this metabolite (10-12). Inhibition of urinary reabsorption of this toxic metabolite 1,5AG by glucosuria can be achieved with empagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, leading to clinical improvement (13). It is shown, that the levels of plasma 1,5AG and intracellular 1,5AG6P decrease after the use of SGLT-2 inhibitors (14). However, as seen in our patient, it might not have a significant effect on infection frequency. It is important to note here that treatment with SGLT-2 inhibitors poses an increased risk of urinary tract infections and hyponatremia (15).

Although the prognosis in many of the inborn metabolic disorders has been so far considered devastating, newer therapies such as enzyme replacement therapies, strict dietary measures, or repurposing of the already present medical therapies can benefit these patients significantly in some forms, leading to improved clinical outcomes and near-normal or normal life expectancies (16). The repurposed application of empagliflozin in the presented patient, originally an antidiabetic agent now considered to be beneficial in a great number of conditions ranging from chronic kidney disease to heart failure, presents a good example (17). Besides all the advantages, it shouldn't be forgotten that this is still an experimental therapy and the use of the agent should always be decided by an experienced clinician, after taking into account the risks mentioned above.

Finally, many of the inborn metabolic disorders are underdiagnosed, as some patients can present with an attenuated phenotype, making estimations of their prevalence in the common population challenging (18). Nevertheless, it is important to recognize these patients and refer them to specialists in order not to delay treatment with the existing treatment modalities and prevent further morbidity and mortality.

Ethics Committee Approval: *N/A*

Informed Consent: *Informed consent was obtained from the patient.*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: H.S.Ö., S.M., M.Ç., Concept: H.S.Ö., E.D.A., S.M., M.Ç., Design: H.S.Ö., E.D.A., S.M., M.Ç., Data Collection and/or Processing: H.S.Ö., E.D.A., S.M., M.Ç., Analysis and/or Interpretation: H.S.Ö., E.D.A., S.M., M.Ç., Literature Search: H.S.Ö., E.D.A., S.M., M.Ç., Writing: H.S.Ö., E.D.A., S.M., M.Ç.*

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

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TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2024;11(2):55-8
DOI: 10.4274/tmsj.galenos.2024.2023-9-2

CASE REPORT

CHRONIC SUBDURAL HEMATOMA CAUSED BY ARACHNOID CYST IN A 12-YEAR-OLD CHILD: A CASE REPORT

Kaan Arslan[1], Alper Er[1], İlayda Eser[1], Atilla Ülkücü[1], Ahmet Tolgay Akıncı[2]

[1]Trakya University School of Medicine, Edirne, TÜRKİYE
[2]Trakya University School of Medicine, Department of Neurosurgery, Edirne, TÜRKİYE

ABSTRACT

This case report details the management of a chronic subdural hematoma associated with an arachnoid cyst in a 12-year-old patient. Following a fall from a tractor, the patient presented with a chronic subdural hematoma and a left temporal arachnoid cyst. The condition was successfully treated using the burr hole drainage technique, with no postoperative complications. This case report highlights the importance for physicians to be aware of the risk of chronic subdural hematoma in patients with arachnoid cysts, especially in high-risk groups. The presence of a cerebral arachnoid cyst facilitated the occurrence of chronic subdural hematoma in young people or children. It also underscores the need for further research to minimize complications and reduce the risk of recurrence.

Keywords: Arachnoid cysts, chronic subdural hematoma, closed head trauma

INTRODUCTION

Chronic subdural hematoma (CSDH) represents a meningeal pathology characterized by an enduring accumulation of blood and its degenerative products on the surface of the brain (1). CSDH is predominantly observed in elderly patients, and the primary etiology is attributed to head trauma. Apart from trauma, non-traumatic causes can also contribute to the development of CSDH (2). The presenting symptoms of CSDH can vary and the most common symptoms are headache, gait disturbance, hemiparesis, and cognitive problems. The prognosis of patients with CSDH is worse when it is accompanied with seizures or low Glasgow Coma scale scores (3). When it comes to determining the internal structures and the size of CSDH, magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) and can also be helpful with the diagnosis of bilateral isodense CSDH, which is difficult to detect by CT (4).

Prior studies have posited that arachnoid cysts (ACs) could potentially serve as a risk factor for CSDH, particularly among children and young adults (5). It is stated that the presentation of CSDH together with subdural hemorrhage is rare (6). However, the mechanistic pathway underlying AC-associated CSDH remains unclear, with a few hypotheses proposed thus far (7). Concurrently, the surgical treatment strategies for CSDH vary, leading to different outcomes and postoperative complications (8). This case report discusses the experience of a 12-year-old CSDH patient with a left temporal AC, managed with a single burr hole craniotomy. We aim to augment the limited body of literature on pediatric CSDH cases associated with AC following head trauma and present the post-treatment prognosis of our patient.

CASE REPORT

A 12-year-old male patient presented to Trakya University Hospital Neurosurgery Department following a fall from a tractor approximately two months prior, experiencing persistent headaches. His physical and neurological examinations revealed no deficits or pathological findings. However, an MRI scan at the

Address for Correspondence: İlayda Eser, Trakya University School of Medicine, Edirne, TÜRKİYE
e-mail: ilaydaeserr@hotmail.com
ORCID iD of the authors: KA: 0009-0002-8048-9960; AE: 0009-0004-1496-8941; İE: 0009-0003-0148-8183; AÜ: 0000-0003-2820-2686; ATA: 0000-0002-9937-076X
Received: 30.01.2024 Accepted: 01.06.2024

Cite this article as: Arslan K, Er A, Eser İ, Ülkücü A et al. Chronic subdural hematoma caused by arachnoid cyst in a 12-year-old child: a case report. Turk Med Stud J. 2024;11(2):55-8.

referring medical center demonstrated a left temporal AC, an ipsilateral subdural hematoma, and a midline shift (Figure 1).

The laboratory results of the patient revealed no abnormalities. After completing routine preoperative preparations, a left parietal burr hole was drilled. Upon incision of the dura, a high-pressure "motor oil-like" fluid, consistent with CSDH, was extruded (Figure 2). The subdural space was thoroughly irrigated with saline, and a subdural drain was placed. No intervention was carried out on the AC.

The patient experienced an uncomplicated postoperative period. His neurological examinations were consistently unremarkable. The postoperative CT and MRI scans exhibited complete evacuation of the hematoma and rectification of the midline shift (Figures 3, 4). The post-surgery follow-up laboratory results for the patient were within the normal range. The patient was discharged on the fourth postoperative day in a stable condition. Postoperatively, a regimen of 500 mg levetiracetam twice daily was administered for antiepileptic prophylaxis. An eight-month follow-up revealed no complaints or complications. Following a normal electroencephalogram, the antiepileptics were ceased.

DISCUSSION

Several methods are commonly employed for the diagnosis and further investigation of CSDH, as well as different aspects of MRI and CT findings and advantages (4). In patients where ACs are identified through radiological imaging, it is recommended that they undergo regular examinations and periodic radiological imaging (7). CSDH is predominantly diagnosed via CT scans. Although most lesions appear hypodense, isodense or mixed-density lesions may also be present. Calcified CSDHs, rarely observed, can mimic calvarial masses, making contrast-enhanced imaging the preferred choice for differential diagnosis (4).

Magnetic resonance imaging offers more sensitivity than CT in assessing the size and internal structures of CSDHs. It can also detect fresh bleeding and changes in hemolysis and hemoglobin. Specifically, contrast MRI is adept at identifying neomembranes and clots, while diffusion MRI proves more beneficial in detecting infected subdural hematomas (4).

Despite CT scans being the initial test typically administered, MRI holds superiority in distinguishing bleeding within the arachnoid cyst from a subdural hematoma. Furthermore, MRI is highly recommended for detecting small AC in pediatric patients diagnosed with CSDH (9).

Existing literature provides various surgical interventions for managing CSDH associated with AC (2, 5, 7, 9-13). Among these, the burr hole drainage technique we employed in our case has been recommended as a viable first-line treatment option, requiring no intervention on the AC membrane (5, 9-11). Some studies have also reported success with the fenestration

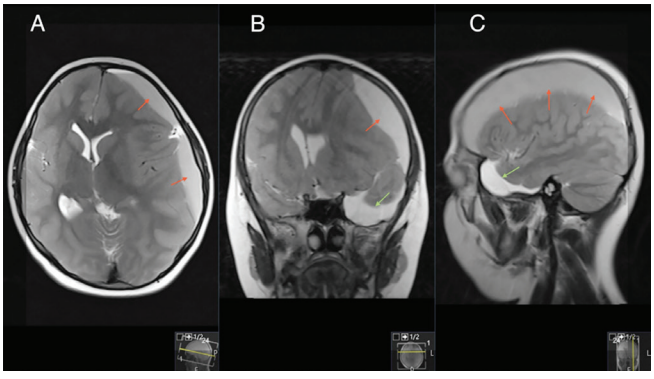

Figure 1: Preoperative magnetic resonance imaging in the axial (A), coronal (B), and sagittal (C) planes.
Red arrows: The subdural hematoma, Green arrows: The arachnoid cyst

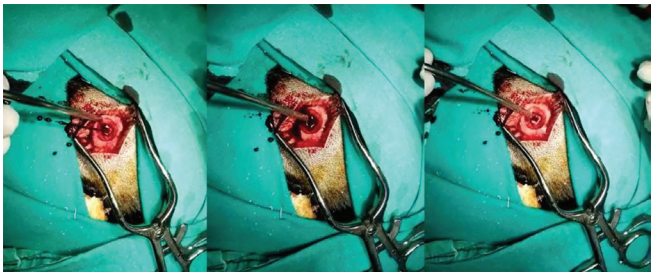

Figure 2: The evacuation of the chronic subdural hematoma through a burr hole.

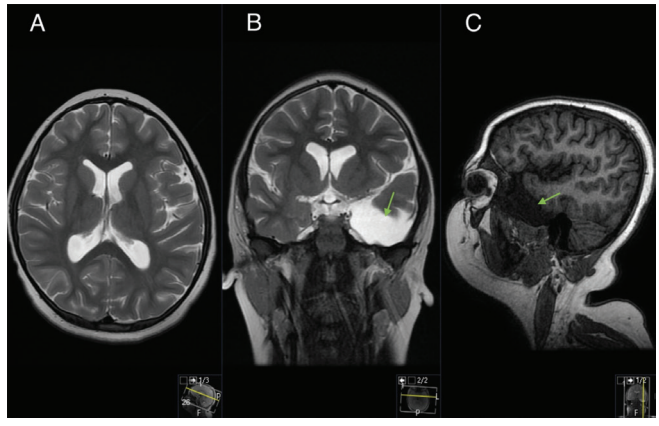

Figure 3: Postoperative magnetic resonance imaging in the axial (A), coronal (B), and sagittal (C) planes.
Green arrows: The arachnoid cyst

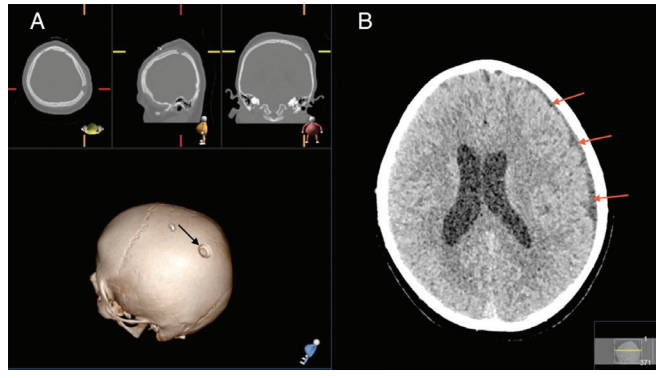

Figure 4: Postoperative computerized tomography, (A) 3D reconstruction, (B) axial section.
Black arrow: The burr hole, Red arrows: The subdural space

of the cyst membrane (7, 11). Our patient experienced favorable results from the burr hole drainage technique, aligning with findings from similar cases in the literature (5).

Recent research has indicated that using drainage can decrease the recurrence of CSDH. The choice of drain type appears to matter. Both the subperiosteal and subdural drains are highly effective. Even though the mortality rate and postoperative complications are lower in subperiostal drainage, there is a higher rate of recurrence in subperiostal drainage when compared to subdural drainage (4). Additionally, some evidence suggests that employing the double burr hole technique is linked with a reduction in postoperative recurrence rate and a shorter duration of hospital stay (10).

The literature has some debate regarding optimal postoperative head positioning. The incidence of postoperative complications, such as atelectasis, pneumonia and deep vein thrombosis are the same in both the 30°-40° sitting position and supine position but in the upright head position there is a higher rate of recurrence (4).

Risk factors for CSDH have been identified as direct or indirect head traumas, chronic alcohol consumption, and anticoagulants and antiplatelet drugs (14). However, the impact of anticoagulant use on CSDH recurrence is disputed (15, 16). Other identified risk factors include coagulopathies, cerebrospinal shunting, hypertension, male gender, and advanced age (14). Head trauma is the most substantial risk factor for both young and elderly patients (9, 12). Meanwhile, CSDH without head trauma has been reported to carry a higher mortality rate, particularly in elderly patients (17). That, however, remains a topic of debate.

Arachnoid cysts are typically congenital in their presentation (9). Various sources also suggest that they originate from the meninges during embryological development (11).

In considering the relationship between AC and CSDH and the mechanism that underlies this relationship, two hypotheses are primarily accepted. The first posits that a change in cerebrospinal fluid flow triggered by mild trauma can increase the arachnoid cyst. That can then cause the rupture of bridging vessels or vessels in the cyst walls. Evidence indicates that pressure is transmitted more rapidly in cyst fluid than in normal subarachnoid cerebrospinal fluid. The second theory suggests ACs have less compliance than normal brain tissue, which results in post-traumatic hemorrhage. This hemorrhage, in turn, forms subdural hematomas in bridging vessels (9).

Our patient, a 12-year-old male, had a history of trauma due to a fall from a tractor. The presence of an AC, another risk factor, could have increased the risk of hemorrhage following trauma, potentially contributing to hematoma formation (9, 12, 18). AC can either present asymptomatically or cause symptoms due to enlargement of the AC and can exert mass effect on surrounding neural structures (19). In terms of symptoms and signs, CSDHs can range from being asymptomatic to presenting with a variety of symptoms such as headaches, seizures, memory lapses, confusion, difficulties in swallowing and walking, as well as weakness or numbness in the legs, face, and arms (4). On the contrary, ACs are typically asymptomatic, with skull asymmetries serving as potential indicators of their presence (7, 11).

As such, physicians need to be aware of the risk of CSDH in patients with a known history of AC. This risk is particularly relevant to athletes and individuals involved in martial arts, such as taekwondo, as these activities pose a high risk of head injuries (9). Physicians should consider CSDH associated with AC in young athletes, especially the ones present with concussion like symptoms. Even though these two pathologies tend to occur in different age groups, there is a risk for them to present together after a mild head trauma (6). Discussing potential protective measures implemented during these activities may prove beneficial.

From an epidemiological perspective, CSDHs are estimated to occur in 1.7 to 20.6 per 100,000 individuals annually (7). While CSDHs are generally observed in the elderly, they can also be present in younger individuals. Literature reveals that they are seldom seen in infants. However, bilateral CSDHs in infants should raise suspicion of intentional trauma such as physical abuse. CSDHs typically occur on the most curved region of the frontal or occipital convexity of the brain. Despite their usual occurrence in the convex areas of the brain, they can also be interhemispheric (4). ACs, on the other hand, are reported to occur in 0.7-1.7% of the population (7). They are commonly observed in children and are often localized in the middle fossa (9).

There may be significant contributions to the literature by exploring the potential benefits of arachnoid cyst removal and the impact of a cyst-related intervention on the treatment prognosis of subdural hematoma. Moreover, the pathophysiology of CSDHs may involve rupture of the bridging veins and volume expansion of the existing hematoma due to the addition of cerebrospinal fluid (9, 12). In AC-related CSDHs, hypotheses center on the rupture of the vessels in the AC's outer membrane and the subdural space if the cyst fluid in the AC transmits the trauma (9, 12, 18). Further understanding of the mechanism of AC-related CSDH may greatly aid in developing treatment plans to eliminate the source and prevent potential treatment complications. There is also an ongoing debate about optimal postoperative head positioning, and further research is needed to identify a position that minimizes complications without increasing the risk of recurrence (4).

Ethics Committee Approval: *N/A*

Informed Consent: *Informed consent was obtained from the patient.*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: A.Ü., A.T.A., Concept: K.A., A.E., İ.E., A.Ü., A.T.A., Design: K.A., A.E., İ.E., A.Ü., A.T.A., Data Collection and/or Processing: K.A., A.E., İ.E., A.Ü., A.T.A., Analysis and/or Interpretation: K.A., A.E., İ.E., A.Ü., A.T.A., Literature Search: K.A., A.E., İ.E., A.Ü., A.T.A., Writing: K.A., A.E., İ.E., A.Ü., A.T.A.*

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

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TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2024;11(2):59-61
DOI: 10.4274/tmsj.galenos.2024.2023-7-1

CASE REPORT

CAUSE OF PERSISTENT CHEST PAIN: TWO MYOCARDIAL BRIDGES IN A YOUNG WOMAN

Zeynep Rana Yıldız[1], Servet Altay[2]

[1]Trakya University School of Medicine, Edirne, TÜRKİYE
[2]Trakya University School of Medicine, Department of Cardiology, Edirne, TÜRKİYE

ABSTRACT

Myocardial bridging is a congenital anatomical anomaly characterized by a coronary artery with an epicardial course that dips into the myocardial tissue before resurfacing on the heart's surface. While it is commonly observed in the left anterior descending coronary artery, it typically occurs in a single coronary artery or a segment thereof. Myocardial bridging is generally asymptomatic and benign; however, in some cases, it can present with symptoms such as chest pain, arrhythmias, myocardial infarction, coronary vasospasm, syncope, and even sudden death. In our case, a patient admitted to our hospital with persistent chest pain for 6 months had myocardial bridges involving two different segments of the left anterior descending artery. Therefore, myocardial bridges should be considered in young patients presenting with angina pectoris.

Keywords: Angina pectoris, coronary artery, myocardial bridging

INTRODUCTION

Coronary arteries typically run through the outer layer of the heart known as the epicardium. However, in some cases, branches of the coronary arteries traverse the myocardial muscle tissue before returning to the heart's surface. This congenital situation is referred to as myocardial bridging (1).

Myocardial bridging can occur in any coronary artery, including the right coronary artery (RCA), left anterior descending artery (LAD), circumflex artery, and their branches, but it is mostly present in LAD (2, 3).

Although it is usually benign, patients can present with serious complications such as ischemia, syncope, ventricular tachycardia, arrhythmia, cardiac arrest, and even sudden death (4-7).

In this article, we discuss a 36-year-old female patient presenting with exercise-induced angina pectoris.

CASE REPORT

A 36-year-old female experiencing exertional chest pain for the past six months, classified as class II according to the Canadian Cardiovascular Society angina severity classification, was admitted to our hospital. She had no history of smoking, hypertension, diabetes mellitus, hyperlipidemia, or family history of cardiovascular diseases. The patient had been started on metoprolol 50 mg, acetylsalicylic acid (ASA) 100 mg, and atorvastatin 20 mg at an external center due to her symptoms.

On admission, her blood pressure was 120/82 mmHg, and her heart rate was 86 beats per minute. Physical examination of the heart and respiratory system revealed normal findings, with no cardiac murmurs and pulmonary edema. The baseline electrocardiogram documented a sinus rhythm at 80 beats per minute, with no atrioventricular conduction irregularities or repolarization abnormalities. A transthoracic echocardiogram showed normal results.

Her levels of troponin, hemoglobin, thyroid function, lipid panel, and serum creatinine were all normal. An exercise stress test was performed, which revealed a 0.5 mm ST segment depression in the infero-lateral leads, and the patient reported non-specific chest pain. Considering the mismatch between the symptoms and the exercise stress test findings, a myocardial perfusion scintigraphy was performed.

Address for Correspondence: Zeynep Rana Yıldız, Trakya University School of Medicine, Edirne, TÜRKİYE
e-mail: zeynep.yildiz99@yahoo.com
ORCID iD of the authors: ZRY: 0000-0003-4488-7451; SA: 0000-0001-7112-3970.
Received: 29.09.2023 Accepted: 12.06.2024

Cite this article as: Yıldız ZR, Altay S. Cause of persistent chest pain: two myocardial bridges in a young woman. Turk Med Stud J. 2024;11(2):59-61.

Following the detection of 10% ischemia in the anteroseptal wall via myocardial perfusion scintigraphy, coronary angiography was conducted. The angiography revealed two myocardial bridges located in the proximal and middle segments of the LAD artery. These bridges caused a critical 95% stenosis during systole, a phenomenon known as the milking effect (Figure 1a). Interestingly, during diastole, there was a significant improvement in the stenosis of the tunneled coronary artery segment (Figure 1b). Notably, the pre-stenotic proximal and distal segments had no pathological findings. The lengths of the myocardial bridge segments were measured at 22 mm in the proximal segment and 15 mm in the middle segment.

Subsequently, we discontinued statin and ASA therapy and adjusted the metoprolol dosage based on her blood pressure and heart rate. During the follow-up appointments, a decrease in angina was observed.

DISCUSSION

Myocardial bridging is a congenital anomaly of the coronary arteries. It occurs when a segment of the coronary artery traverses the myocardial tissue, forming a "bridge" of muscle (3).

The historical background of myocardial bridging reveals early observations, with the first descriptions dating back to 1737 and 1805. In 1951, the first examination of myocardial bridges in autopsy was performed, followed by radiological descriptions in 1960 (8).

The prevalence of myocardial bridging varies in different studies. Autopsy series have reported frequencies ranging from 15% to 85%, while angiographic procedures show lower rates, ranging from 0.5% to 16% (1, 9, 10).

In retrospective studies conducted by Akyol et al. (11) and Oylumlu et al. (12) in Türkiye, myocardial bridging was found to be more common in men than in women, with mean ages of 59.3 and 57.1, respectively. However, our patient's age was below these mean ages, which is unusual. Male predominance has been reported in autopsy and angiographic studies (6, 8).

Myocardial bridges can also be categorized based on their depth in the myocardial tissue, with the superficial type being more prevalent, accounting for approximately 75% of cases (2, 13).

While myocardial bridging can occur in any coronary artery, it is most frequently observed in the middle segment of the LAD (2). Various studies report different incidences; for instance, Yukio et al. (14) reported 68.1% of cases in the middle segment of the LAD, while Loukas et al. (8) found different percentages for various arteries (14-16). In a necropsy study Ferreira et al. (13) conducted, 50 hearts with myocardial bridges were examined, 35 of the 50 hearts had single myocardial bridge and only appeared on LAD, 10 of them had two myocardial bridges and 5 of them had three. Such variations may arise due to population differences and study methodologies. In our case, we identified two consecutive myocardial bridges causing sequential critical stenosis in the LAD coronary artery, which is a rare occurrence.

The RCA is the second most common vessel and has been reported between 1-18.5% (8, 11, 14).

There are various methods to make a diagnosis of myocardial bridging. Multidetector computed tomography coronary angiography, conventional coronary angiography, and intravascular ultrasound are methods used to diagnose myocardial bridging (9). Non-invasive techniques, such as nuclear stress tests and stress echocardiography, or invasive techniques, such as fractional flow reserve, can be used to evaluate whether myocardial bridges cause ischemia. In our case, we diagnosed the patient, who had presented to our hospital with a six-month history of exertional angina, using coronary angiography.

The proximal segment of the myocardial bridge can be associated with atherosclerosis due to mechanical and blood flow changes (16). Artery compression during systole leads to hemodynamic alterations, and substances like lipids and mucopolysaccharides conglomerate to the coronary artery segment proximal to the myocardial bridge. Additionally, higher expression of vasoactive agents was detected in the segment proximal to the myocardial bridge (16, 17).

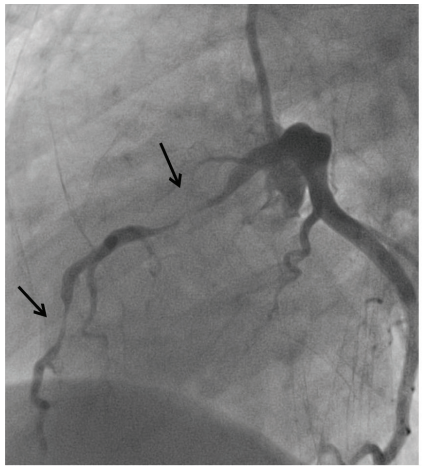

Figure 1a

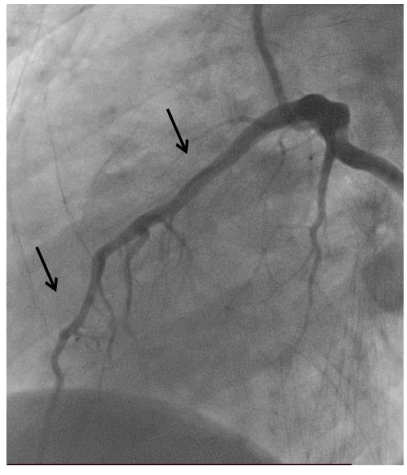

Figure 1b

Figure 1: Myocardial bridging was identified on coronary angiography.
Arrows: Myocardial bridging was stenosed about 95% during systole in proximal and middle segments and recovered during diastol.

Myocardial bridging has traditionally been considered a benign condition, but in some cases, compression during systole on a portion of the coronary artery can lead to blood flow obstruction, resulting in various complications. These complications may include myocardial infarction, arrhythmias, exertional angina, vasospastic angina, acute coronary syndrome, syncope, and even sudden death (2, 16-18). Other potential causes such as microvascular angina, myocardial infarction with non-obstructive coronary arteries, vascular spasm, spontaneous coronary dissection, and coagulation disorders should be considered in the differential diagnosis for individuals in this age group.

Pharmacological treatment options for symptomatic patients with myocardial bridging include beta-blockers as the first choice, calcium channel blockers, nitrates, ivabradine, and antiplatelet therapy. From the perspective of long-term prognosis, the effectiveness of stent implantation at the site of a myocardial bridge is not favorable, and thus, coronary stents are generally not preferred. Coronary artery bypass grafting and surgical myotomy may be the final treatment options for patients with refractory symptoms and signs (16, 19, 20).

The long-term prognosis for patients with myocardial bridging remains a subject of debate. Some studies suggest that patients with myocardial bridging, in the absence of other cardiovascular diseases have a good long-term prognosis while others indicate an elevated risk of non-fatal myocardial infarctions and adverse cardiac events associated with myocardial bridging (21, 22).

In conclusion, we have presented this case due to its unique characteristics, which are less commonly reported in the literature. These include the patient's young age, female gender, and the presence of two distinct myocardial bridges within the same artery. This case emphasizes the importance of considering atypical presentations and diagnostic challenges in the management of coronary artery disease, particularly in young and female patients. Further research and documentation of such cases may contribute to comprehend the spectrum of cardiovascular pathologies and their management strategies.

Ethics Committee Approval: *N/A*

Informed Consent: *Informed consent was obtained from the patient.*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Concept: S.A., Design: S.A., Data Collection or Processing: Z.R.Y., Analysis or Interpretation: S.A., Literature Search: Z.R.Y., Writing: Z.R.Y.*

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

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TMSJ
TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2024;11(2):62-5
DOI: 10.4274/tmsj.galenos.2024.2024-3-1

CASE REPORT

HEMOPTYSIS SECONDARY TO PULMONARY ARTERY-TO-INTERCOSTAL ARTERY FISTULA: A CASE REPORT

Ali Doruk Kurt[1], Beyza Yılmaz[1], Fazlı Yanık[2]

[1]Trakya University School of Medicine, Edirne, TÜRKİYE
[2]Trakya University School of Medicine, Department of Thoracic Surgery, Edirne, TÜRKİYE

ABSTRACT

Intercostal artery-pulmonary artery fistulas can be congenital or may occur due to trauma, neoplasms, and inflammation. These fistulas are usually asymptomatic, but they may occasionally give rise to emergencies presenting with symptoms such as hemoptysis. This case report presents a 35-year-old male patient with a history of acute tubular necrosis, chronic kidney failure, and tuberculosis who is receiving hemodialysis treatment. The patient, who was admitted to the hospital with an episode of hemoptysis lasting three days, underwent chest tomography and angiography examinations, and it was revealed that there was a fistula between the branches of the left pulmonary artery and the left eighth intercostal artery. This rare fistula could have caused potentially fatal complications in our dialysis patient receiving anticoagulation therapy. The interventional radiology team decided to choose surgical treatment after evaluating the patient in a council meeting, and the patient was taken into surgery. Surgical pulmonary resections can be successfully performed in the curative treatment of this rare disease.

Keywords: Arterio-arterial fistula, hemoptysis, tuberculosis

INTRODUCTION

Intercostal artery-to-pulmonary artery fistulas are congenital or acquired abnormal connections between the systemic artery and the pulmonary artery. This rare condition can be caused by trauma, neoplasms, or inflammation. Since the disease is usually asymptomatic, it is usually detected incidentally. In addition, the disease can cause symptoms in the form of hemoptysis, dyspnea, and heart failure (1).

A contrast-enhanced computed tomography (CT) scan, angiography, and radionuclide angiocardiogram are used for a definitive diagnosis (2-4). Additionally, magnetic resonance velocity mapping, which is a non-invasive imaging technique of great interest in guiding the diagnosis of arteriovenous fistulas, can also be used. Selective arterial angiography is useful both in confirming the diagnosis and in treatment (5).

The treatment method alternatives include embolization of the responsible vessels, ligation of fistulas, or pulmonary lobectomy (2, 3). Post-treatment follow-up is necessary as the disease can cause adverse hemodynamic effects, bacterial vegetation, and rupture (6). In this article, we aim to present a very rare case of connection between the intercostal artery and the pulmonary artery.

CASE REPORT

A 35-year-old male patient was admitted to our hospital due to massive hemoptysis that had been going on for three days. He also reported that he had been experiencing coughing and left-side chest pain for four to five months. Physical examination findings were normal, and the patient's history revealed that acute tubular necrosis had developed after six months of tuberculosis treatment, followed by the onset of chronic kidney failure. The patient stated that he had been receiving hemodialysis treatment for two years. Approximately 200 cc of hemoptysis not resulting in asphyxia was identified. A chest CT scan was performed on the patient who applied to the emergency department with massive hemoptysis. Considering

Address for Correspondence: Ali Doruk Kurt, Trakya University School of Medicine, Medical Student, Edirne, TÜRKİYE
e-mail: adorukkurt@trakya.edu.tr
ORCID iD of the authors: ADK: 0009-0003-7615-0910; BY: 0009-0003-3352-3342; FY: 0000-0002-8931-5329
Received: 23.03.2024 Accepted: 28.06.2024

Cite this article as: Kurt AD, Yılmaz B, Yanık F. Hemoptysis secondary to pulmonary artery-to-intercostal artery fistula: a case report. Turk Med Stud J. 2024;11(2):62-5.

the possibility of arterio-arterial fistula (AAF), the patient was admitted to the intensive care unit for follow-up. In the angiography, abnormal high-speed flow was detected in the fistula between the left pulmonary artery branches and the left eighth intercostal artery (Figure 1). Furthermore, a connection with the common basal artery was observed at the level of the intercostal artery fissure. Bleeding was controlled with embolization, then the patient developed pneumonia. During intensive care follow-up, a catheter was inserted to administer tazobactam for pneumonia treatment. Subsequently, due to the patient's persistent fever and progression observed in the posterior-anterior chest X-ray, along with a potential catheter infection, the antibiotic regimen was altered to linezolid and meropenem for two weeks. The interventional radiology team checked on the patient after their antibiotic treatment was discontinued. As the condition remained stable throughout follow-ups, the patient was discharged with a recommendation for a follow-up appointment at the outpatient clinic 10 days later. The case was evaluated in a multidisciplinary pulmonary council with the participation of a thoracic surgeon, pulmonologist, medical oncologist, nuclear medicine specialist, and radiologist. The interventional radiology team found re-endovascular embolization of the fistula risky due to the potential to cause lung infarction and decided that surgical treatment would be appropriate for the patient. Fiberoptic bronchoscopy was performed before surgery and hemoptysis was observed from the lower lobe bronchus of the left lung. In addition, lobectomy was preferred as a surgical procedure because the anastomosis was seen at the level of the common basal artery and intercostal artery fissure in the thorax CT.

Four months after the attack of hemoptysis, the patient was operated on under general anesthesia with left selective intubation in the right lateral decubitus position. Using a left posterolateral thoracotomy incision, the thorax was accessed through the fifth intercostal space. During exploration, an intercostal artery connection was detected in the posterior part of the left lower lobe. When the artery was seen extending into the parenchyma, the fistula was closed using a LigaSure device, and it was decided to perform a left lower lobectomy. Adhesions in the lung were separated using blunt and sharp dissection techniques. Subsequently, the pulmonary ligament was released, completing the pneumolysis. The fissure was separated with blunt and sharp dissection. The inferior pulmonary vein was ligated and divided. The branches of the pulmonary artery supplying the lower lobe were ligated and divided. A laceration incurred during pneumolysis was repaired. After controlling bleeding and leaks, a thoracic drain was placed, and the layers were closed. Early complications were not detected. Furthermore, the pathological examination of the left lower lobectomy specimen was performed. The totally resected specimen, measuring 16.5x9x2.8 cm, had a pink cut surface. Macroscopically, no mass lesions were detected. Subpleural hemorrhagic areas measuring 4.2x3.5 cm were observed on the anti-hilar side of the outer surface. In microscopic examination, acid-fast bacilli were negative and there was no growth in culture. No fistula was detected in the pathological specimen. No neoplasm was found in the examination. The patient was discharged with satisfaction on the sixth postoperative day.

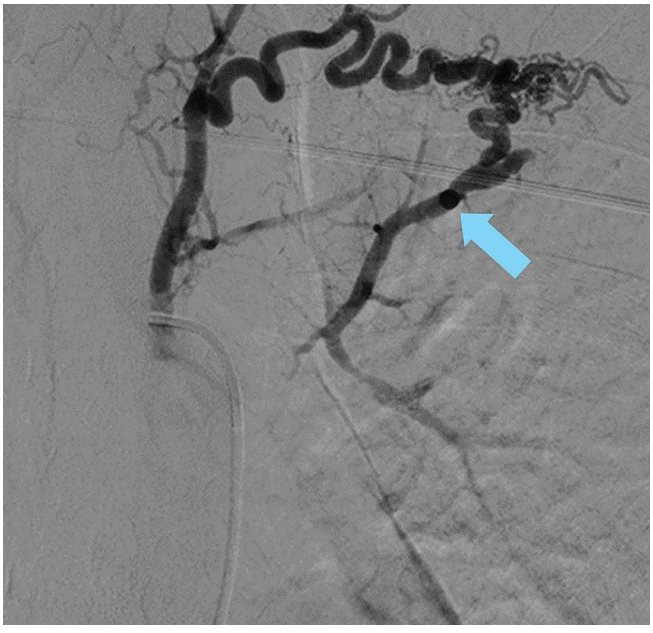

Figure 1: Angiography view of the AAF between the left pulmonary artery branches and the eighth intercostal artery, marked with the blue arrow.
AAF: Arterio-arterial fistula

In the second month after surgery, the patient was admitted to the emergency department again with hemoptysis. During bronchoscopy, minimal bleeding due to irritation was observed in the upper lobe of the right main bronchial system. We did not see any bleeding areas around the bronchial stump that could cause hemoptysis. After confirming the absence of active bleeding, 0.5 g tranexamic acid was administered to the patient three times a day via infusion for five days. Subsequently, the administration was converted to an intravenous push as needed, and the patient was kept under supervision. Additionally, piperacillin-tazobactam 3x4.5 g antibiotic treatment was administered for seven days. Afterward, no pathology was found in the thorax CT. He was discharged due to the improvement of his medical condition. No complaints were observed in the postoperative period. The patient is still being followed up without hemoptysis in the sixth postoperative month.

DISCUSSION

In a typical situation, there is no direct connection between the intercostal artery and the pulmonary artery. However, abnormal connections called fistulas may occur due to trauma, infection, idiopathic factors, and congenital causes (6, 7). These triggering factors cause blood to form a fistula by following the fistula path with lower resistance instead of capillaries (8). These fistulas frequently cause no symptoms and are often found incidentally during medical investigations. Rarely, in cases of rupture of the fistula, massive hemoptysis can occur in the patient. Hemoptysis is a symptom that can be described

as bleeding from the trachea-bronchial system during coughing. Massive hemoptysis is defined as bleeding of more than 150 mL in 24 hours or bleeding rate >100 mL/hour (9). This may be caused by conditions, including tuberculosis, bronchiectasis, or arterio-venous malformations (10). This can lead to life-threatening complications such as airway obstruction, hypoxia, or hemodynamic instability (9). Therefore, it is necessary to take this situation seriously and start treatment immediately. We think that hemodialysis played an important role in the massive hemoptysis experienced by our patient with chronic renal failure. This was primarily attributed to the fact that the anticoagulants administered to the patient increased the blood flow rate.

To diagnose a pulmonary-intercostal artery fistula in a patient experiencing hemoptysis, chest X-ray and CT angiography are used as diagnostic methods. In these techniques, lung infiltration due to the indentation under the rib and signs of bleeding can be observed. However, these techniques cannot conclusively establish the diagnosis. Digital subtraction angiography is a safe diagnostic method that determines the correct location of intercostal-pulmonary artery fistulas and clearly visualizes the presence and size of these fistulas (7). Additionally, in life-threatening hemoptysis, the use of CT together with fiberoptic bronchoscopy can provide more effective results (11). Fiberoptic bronchoscopy allows visualization of the bleeding area and can provide treatment if bleeding continues (12). The use of fiberoptic bronchoscopy becomes even more important in ensuring airway control and in patients with bilateral lung disease (11).

In a study involving 348 patients treated for either moderate recurrent or life-threatening hemoptysis with bronchial artery embolization, active tuberculosis was found in 27% of these patients and tuberculosis sequelae were found in 29.9% (13). During angiography performed on these patients, it was observed that 14% of the patients had fistulas between the pulmonary artery and intercostal artery, as in our case (13).

When we examined the literature from a pathological perspective, we saw that patients with previous tuberculosis disease had conditions that resulted in fistula formation, recurrent hemoptysis, and death due to a decrease in functional lung parenchymal volume (14). These results confirmed that tuberculosis sequelae can cause fistula formation and recurrent hemoptysis, even if there is no active tuberculosis as in our patient (14).

In a literature review, 15 intercostal-pulmonary artery fistula cases were compiled. Tuberculosis played a role in three of these patients with known etiologies. The inflammatory reaction can cause increased pulmonary capillary permeability in the lungs and the infiltration of blood cells into the alveoli due to *Mycobacterium tuberculosis* toxins and massive sensitizers. Necrolysis of lesion tissue due to caseous necrosis can lead to erosion and vessel damage. In the circular veins around the bronchial arteries, bronchiectasis and occlusion occur together (7).

As a result, inflammation and angiogenesis caused by tuberculosis, bleeding diathesis caused by hemodialysis, and heparin used during dialysis may have caused hemoptysis in our patient. However, the fact that fistula cases in the reported literature are detected at a young age also indicates that these may be rare congenital anomalies (15). In our patient, as a source of recurrent hemoptysis after surgery, no fistula or any cause was found. Since the condition did not recur after medical treatment, further examination could not be performed.

Embolization treatment is the preferred treatment method in AAFs because it is less invasive, does not require anesthesia, and causes less trauma. However, embolization has a high risk of recurrence. Various surgical treatments such as lobectomy, segmentectomy, and pneumonectomy have been reported. To preserve normal lung parenchyma, vascular dissection and peripheral lung resection can be performed (16). In life-threatening cases, wedge resection may be preferred as a fast and simple method to stop massive hemoptysis (17). Since our case carries a risk of recurrence, lobectomy was preferred as the treatment method. Surgical treatment is used in recurrent cases and multiple vascular abnormalities. This was the situation with our patient, taken into surgery and successfully discharged after undergoing a left lower lobectomy.

CONCLUSION

Pulmonary AAF is a very rare situation that can cause life-threatening complications. Selective arterial embolization is necessary both to confirm the diagnosis and to provide embolization to appropriate patient groups. Surgical pulmonary resections can be successfully performed in curative treatment.

Ethics Committee Approval: *N/A*

Informed Consent: *Informed consent was obtained from the patient.*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: F.Y., Concept: A.D.K., B.Y., Design: A.D.K., B.Y., Data Collection or Processing: A.D.K., B.Y., Analysis or Interpretation: A.D.K., B.Y., F.Y., Literature Search: A.D.K., B.Y., Writing: A.D.K., B.Y.*

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

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