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"Turkish Medical Student Journal (TMSJ) is the first scientific journal in Turkey to be run by medical students and to publish works of medical students only. In that respect, TMSJ encourages and enables all students of medicine to conduct research and to publish their valuable research in all branches of medicine.

Turkish Medical Student Journal publishes researches, interesting case reports and reviews regarding all fields of medicine. The primary aim of the journal is to publish original articles with high scientific and ethical quality and serve as a good example of medical publications for those who plan to build a career in medicine. TMSJ believes that quality of publication will contribute to the progress of medical sciences as well as encourage medical students to think critically and share their hypotheses and research results internationally.

The journal is published every four months. The language of the publication is English.

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Turkish Medical Student Journal is an independent, non-profit, peer-reviewed, international, open-access journal; which aims to publish articles of interest to physicians, scientists, and medical students. TMSJ is published three times a year, in February, June, and October by Trakya University. The language of publication is English. Correspondent authors of the articles should be a medical student.

Turkish Medical Student Journal publishes original researches, interesting case reports, and reviews regarding all fields of medicine. All of the published articles are open-access and reachable on our website. The primary aim of the journal is to publish original articles with high scientific and ethical quality and serve as a good example of medical publications for stimulating students, doctors, researchers. Our mission is to feature quality publications that will contribute to the progress of medical sciences as well as encourage medical students to think critically and share their hypotheses and research results internationally.

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**Beliz Koçyiğit**

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# PREVENTION OF CARDIOVASCULAR DISEASE: A NUTRIGENETIC APPROACH

Betül Filiz Doğan<sup>1</sup> , Buse Ataçer<sup>2</sup> , Ceyda Kantur<sup>2</sup> , Melis Ocak<sup>2</sup> 

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## ABSTRACT

Cardiovascular diseases are the leading cause of death worldwide. Besides genetic factors, environmental factors also contribute to their etiology. Nutrigenetics provides the opportunity to prevent or reduce the incidence of many diseases. In this review article, we investigated the incidence of cardiovascular diseases in relation to nutrigenetics, genotype-specificity, personalized conditions, nutrition, genetic polymorphisms, and environmental factors. We concluded that the genes encoding miRNA, APOB, PCSK-9, SORT1, cytokines, and IFN- $\gamma$  are strongly associated with development and progression of cardiovascular diseases. Through nutrigenetic testing, we can determine the risk factors, identify preventative strategies, and improve the quality of life through personalized nutrition.

**Keywords:** Cardiovascular disease, nutrigenetics, genotype, diet

## INTRODUCTION

Nutrigenetics is a branch of genetics that analyzes the relationship between genetic polymorphisms of individuals and their response to a diet (1). Previous research has suggested that nutrigenetics may be associated with many conditions such as obesity, cardiovascular disease (CVD), and hypertension (1). Nutrigenetics can improve the quality of life for many people and allow us to develop preventative measures for metabolic diseases through analyzing their genomes and providing a personalized diet based on their genetic composition (1).

The human genome consists of almost 3 billion base pairs encoding 30,000 genes and 100,000 proteins (2). Although 99.9% of the genome is identical in humans, about 1,500 base pairs contain polymorphisms (2). Previous genetic studies have identified genetic variants related to obesity and concluded that in addition to environmental and lifestyle

factors, genetic factors strongly correlate with CVD, cancer, diabetes, and osteoporosis (2).

Molecular genetics and pharmacogenetics play an important role in the diagnosis, treatment, and prevention of CVDs (3). Genetic testing is used to determine genetic transmission of and familial predisposition to diseases such as hypertrophic cardiomyopathy and familial hypercholesterolemia (4, 5). Nutrigenetics aims to provide another preventative approach through dietary changes based on one's genome (1).

## NUTRIGENETICS IN DISEASE

Nutrigenetic studies have provided insights into many diseases from obesity to bone disease to CVD (1, 6). Genetic factors play a crucial role in obesity and these genetic variants have been useful in the development of nutrition plans in obesity treatment (7). Similarly, 50-80% of bone diseases are associated with genetic polymorphisms. For instance, vitamin D receptor



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polymorphisms are important in mineral density, calcium, and vitamin D supplementation, while vitamin B and K polymorphisms are not as critically associated (6). Genes related to sodium metabolism have shown that the amount of salt in the diet is associated with hypertension (8).

### Cardiovascular Diseases

Cardiovascular diseases are the leading cause of mortality and disability worldwide but can be preventable through lifestyle and dietary changes (9). Genes interact with nutrients to influence cardiovascular regeneration or repair (10). Polymorphisms in certain genes can predispose individuals to myocardial infarction (MI) and stroke, as well as hypertension, diabetes, and inflammation (11). The genetic risk factors of CVDs are not yet fully determined (12, 13). However, it has been observed that individuals with the E4 allele in the *apolipoprotein E* gene have higher levels of low-density lipoprotein (LDL) in fat intake when compared to other individuals (14). Obesity, sedentary lifestyle, and hyperinsulinemia may also contribute to the risk of CVDs (11).

### Hypertension

Hypertension is one of the most prevalent risk factors for CVDs and its treatment has been shown to reduce the incidence of CVDs (15). In particular, the Framingham Heart Study showed a clear relationship between hypertension and the risk of CVDs (15). Its prevalence increases with increasing age such that prevalence is 7.3% in adults aged 18-39 years, 32.2% in adults aged 40-59 years, and 64.9% in adults aged 60 years and over (16).

There are many mechanisms by which hypertension causes atherosclerosis. An increase in blood pressure can cause an increase in vascular stress (14). Especially in areas of non-laminar flow, there is evidence that increased radial forces cause changes in the endothelial layer that make it more susceptible to movement of LDL into the subendothelium as well as making it easier for monocyte attachment (17). Another contributing mechanism is increased oxidative stress. In hypertension, nicotinamide adenine dinucleotide phosphate-oxidase, xanthine oxidase, and cyclo-oxygenase enzyme systems are activated, and the detoxifying enzyme superoxide dismutase is decreased, resulting in increased availability of superoxide anions, which reduces the availability of nitric oxide and generates pro-inflammatory radicals (18).

### Smoking

A 2005 INTERHEART study examined the risk factors for heart disease, such as smoking and second-hand smoke, as a prospective case-control study in 52 different countries (19). The INTERHEART study showed that the risk of acute MI increased approximately threefold in smokers and was directly proportional to the number of cigarettes smoked (19).

Smoking increases the risk for atherosclerosis and CVDs through inhibition of nitric oxide production (20). Decreased nitric oxide production impairs vasoconstriction and vasodilation due to endothelial dysfunction and causes LDL oxidation, which is an important factor in the development of atherosclerosis (20). Endothelial damage induces adhesion of monocytes and increases the recruitment and migration of monocytes into the subendothelial space, which further advances atherosclerosis (20). In addition to its role in the development of atherosclerotic plaque, it has been shown that smoking increases fibrinogen levels, which increases thrombosis and therefore may cause subsequent clot formation in the ruptured plaque, which causes acute MI (20).

### Obesity

Thirty nine percent of the world's adult population was overweight and 13% were obese in 2016 (21). Obesity may play a role in the formation and progression of adiposity and other metabolic diseases by affecting energy balance and body weight regulation (21).

There is evidence that obesity triggers atherosclerosis (22). Obesity is an inflammatory disease because adipose tissue is a source of proinflammatory adipokines such as tumor necrosis factor alpha, interleukins, monocyte chemoattractant protein-1, resistin, and leptin. These adipokines have effects such as stimulating vascular reactivity, stimulating inflammation, and even coagulation (22). Therefore, obesity is both a risk factor and a risk marker for CVDs, and its increase over the past 20 years makes it an important target for intervention (11).

Having a sedentary lifestyle increases the risk of CVDs (23, 24). One study considered that decreasing lipoprotein lipase activity during sitting resulted in less catabolism of triglycerides and increased plasma triglyceride levels (23). A sedentary lifestyle also decreases endothelial nitric oxide expression caused by low blood flow in the limbs with prolonged sitting (24).

## ROLE OF GENETICS

### Role of MicroRNAs in CVDs

MicroRNAs (miRNAs) are part of the non-coding RNA family, which are associated with gene expression and intercellular communication (25). They play a key role in pathogenicity in many diseases such as MI, inflammation, hypertrophy, and atherosclerosis (26). miRNAs in the cardiovascular system control the functions of muscle cells and vascular endothelial cells, and abnormal expressions of these miRNAs are associated with cardiac dysfunction (27-29).

Previous studies demonstrated that miRNA expression in damaged tissues in patients with CVDs is irregular (27, 30).

In an experiment in mice, severe developmental defects in the heart and blood vessels demonstrated the importance of miRNAs in heart biology through tissue-specific erasure of genes such as Droscha, DGCR8, Argonaute RISC Catalytic Component 2, or Dicer, which are essential for miRNA biogenesis (23). miRNAs became the new biomarker for the diagnosis of CVDs (31).

#### Use of Molecular Genetics in the Diagnosis of CVDs

Genetic tests are used to determine the underlying causes of CVDs (32). To better interpret genetic test results in terms of CVD risk, the patient should be evaluated comprehensively (33). Hereditary features of CVDs are of varying degrees. Although most CVD-associated polymorphisms are polygenic, they can also be monogenic. When monogenic CVD markers are not recognized and treated accordingly, they can lead to serious illness, disability, and even death. Familial hypercholesterolemia is a widespread monogenic disease caused by mutations in the LDL receptor, *apolipoprotein B (APOB)*, and *proprotein convertase subtilisin/kexin type 9* genes with a frequency of 1/200 (32). Another common familial CVD caused by mutations in approximately 11 genes that encode sarcomere proteins is hypertrophic cardiomyopathy (32).

Our knowledge of CVD risk factors and the genetic background of many non-infectious diseases has increased through Genome-wide Association Studies (GWAS). GWAS identified that the single nucleotide polymorphisms (SNPs) that are associated strongest with CVDs are located in the p21.3 region of chromosome 9 in humans (32, 34). Another gene identified by GWAS is Sortilin (*SORT1*) (32). The most important signals indicating the risk of LDL cholesterol causing CVDs are the *SORT1* gene, which also plays a role in determining plasma cholesterol levels, and the *CELSR2/PSRC1/SORT1* gene set (32). Although research on *SORT1* supported its impact on plasma cholesterol levels and identified it as a risk factor in creating MI, its effects are quite complex and still controversial (35).

There is also a complex relationship between dietary habits and gene expression. Studies show that SNPs in nutrigenetics are associated with plasma lipid rates of nutrients consumed. The relationship of homocysteine with folate intake is thought to be a risk factor for MI and stroke (32). Also, it has been determined that homocysteine concentration is high and methylenetetrahydrofolate reductase polymorphism is more pervasive in regions with low folate intake (36).

#### Association of Extracellular Vesicles with CVDs

Membranous structures that carry bioactive substances, such as macronutrients, messenger RNA, and miRNA, are called

extracellular vesicles (EVs). Key sources of these vesicles in the heart are endothelial cells, cardiomyocytes, macrophages, and fibroblasts (37). EVs have an important role in the signaling and function of their target organs. Moreover, EV molecules are helpful for transferrin's protective role in cardiomyocytes (38). EVs enriched with miRNA-30a are released from cardiomyocytes in response to hypoxia-inducible factor1 $\alpha$  to protect the myocardium from damage during hypoxia (39). EVs produced in cardiomyocytes express exclusive cellular markers such as flotillin-1 and caveolin 3, as well as sarcomeric and mitochondrial proteins such as myomyosin, cardiac-type myosin binding protein C, and tropomyosin (40).

EVs release their cargo to target cells by budding from the plasma membranes (41). With the stimulation of the calcium-dependent mechanism in the plasma membrane, substances inside the EV are poured into the extracellular area (42). Calcium ion affects enzymes such as gelsolin and calpain, which are involved in the disintegration of the cytoskeleton and cause an easy release of microvesicles (37).

Hsa-miRNA-208a was identified as one of the specific miRNAs carried by EVs which increased in blood after MI (43). This research suggested that miRNAs could be useful in the diagnosis of MI and circulating RNAs could be useful biomarkers in the diagnosis of CVDs (43). EVs also protect the heart against MI and arrhythmias (37). Due to the aforementioned features of EVs, they have been proposed to be used as a new diagnostic tool in preventing CVDs (35).

#### The Effect of the Calcium-Calmodulin Mechanism on CVDs

Intracellular calcium, which plays a key role as a second messenger in heart contraction, and the accompanying calmodulin (CaM) protein are major signaling mechanisms (44). With each heartbeat, calcium is released and then taken back into the cell, and CaM plays a role in the excitation-contraction mechanism (44, 45). CaM is a highly preserved protein that can interact with about 300 different proteins other than calcium (46). CaM binds four calcium molecules and is involved in the regulation of calcium channels (45). CaM is also important in regulating cellular events such as infection, cell death, cell growth, and immunity (44).

Calmodulin-related genes are present in chromosomes 2, 14, and 19 and encode isoforms of CaM which differ at a single nucleotide level (44). To understand the genetics of MI predisposition, it is necessary to identify the polymorphisms formed in the CaM mechanism (44). These polymorphisms have been associated with serious diseases of the heart such as ventricular fibrillation, catecholaminergic polymorphic ventricular tachycardia, and diseases with different pathologies such as osteoarthritis and adolescent idiopathic scoliosis (44, 47-49).

It has been reported that polymorphism 34T>A in chromosome 19 affecting the CALM3 transcript is more common in patients with familial hypertrophic cardiomyopathy (FHC) and may therefore be a gene that affects FHC (50). As we learn more about the transcriptional mechanism of the excitation-contraction mechanisms in the heart, we can conclude that genetic factors contribute to the predisposition of individuals to disease CVDs (44).

#### Role of Cytokines in the Formation of Atherosclerosis

As aforementioned, atherosclerosis is an inflammatory disorder that has a role in the formation of CVDs (10). The atherosclerotic plaque formation causes the vascular lumen to narrow, while the rupture of this plaque causes the vascular lumen to become blocked completely through thrombus formation (51). Such vascular obstruction can lead to MI (10). The severity of atherosclerosis was found to be related to cytokine genes in studies conducted with patients recovering from MI (52, 53). Cytokines regulate the expression of inflammatory molecules that can cause atherosclerotic plaque rupture, so it has been recommended to use inflammatory cytokine levels to track the clinical course of CVDs (54).

Interferon-gamma (IFN- $\gamma$ ), a proinflammatory cytokine, is secreted from macrophages and is associated with the formation of atherosclerosis. IFN- $\gamma$  stimulates the production of chemokines and cytotoxic molecules from macrophages, and its expression increases in atherosclerosis (10, 55). In the early stages, IFN- $\gamma$  supports the development of atherosclerosis by stimulating the secretion of adhesion molecules from the endothelium. In the late stages, IFN- $\gamma$  works to separate atherosclerotic plaques by speeding up apoptosis and extracellular degeneration of macrophages (10, 56).

Countless SNPs have been found in the *IFN- $\gamma$*  gene localized at 12q24 (10). One example is the IFN- $\gamma$  +874 T/A (rs2430561) polymorphism, which affects the formation and development of atherosclerotic plaques, and can therefore be used as a biomarker candidate for early MI detection (10).

## TARGETED THERAPIES

### Preventative Medicine and Genetics

Health is defined as a state of complete physical, mental, and social well-being (57). Preventive medicine interventions are medical evaluations that reduce the risk of disease and provide early detection and treatment (57). Through genetic diagnostic tests and nutrigenetics, risk factors that may induce diseases can be identified, and preventative measures can be taken with nutrition and lifestyle changes (58). The goals of nutrigenetics include effective individual dietary

strategies to improve quality of life, prevent diseases, and promote wellness (59).

### Individualized Nutrition

Both genetic and environmental factors contribute to development of CVDs, and nutrition has special importance in CVDs. Nutritional interventions that are personalized according to the individual's genetic background may present a new diet-based approach to treat CVDs and improve health outcomes (1). Studies have shown that genetics can be used to identify individuals who are most likely to lose weight, but these findings should be further investigated before wide use (60).

Historically, nutrition interventions were focused on the relationship between nutrient deficiencies and disease but with new studies, there is a potential to improve chronic metabolic disorders through nutrition (61-64). Through nutrigenetics, it is possible to understand the effects of dietary response and nutritional elements on gene expression based on genetic variations (65). However, despite recent advances in nutrigenetics, there are not enough studies about personalized nutrition. Moreover, the cost of genetic testing poses a great challenge to the widespread use of personalized nutrition (63).

### Nutrigenetics in Controlling Inflammation and Cardiovascular Risk Factors

Inflammation underlies a wide spectrum of diseases from CVDs to psychiatric disorders (66). There is evidence that genetic variation can predispose one to increased inflammation and can increase the likelihood of disease development through interactions with environmental factors such as diet (67). The Mediterranean diet is suggested for reducing inflammation and reversing inflammatory diseases (68).

### Nutrigenetics and the Response to the Mediterranean Diet

As the world population ages, the prevalence of CVDs is also increasing (69). Along with medical treatment, lifestyle changes are also very important in the treatment process (70, 71). Research shows that a diet rich in plant sterols is important in maintaining good health (72).

Previous studies have shown that the Mediterranean diet protects the heart and overall health (73). The traditional Mediterranean diet is characterized by a large consumption of fruits and vegetables, unrefined grains, nuts, fish, legumes, olive oil, moderate consumption of wine, preferably with main meals, and low intake of dairy products and meat (74). The protective effects of the Mediterranean diet are revealed by dietary fiber, unsaturated fatty acids, antioxidants, and bioactive components (75). To get the best results from the Mediterranean diet; cultural, genetic, and socioeconomic factors should be considered (74).



## Nutrigenetics Challenges

For nutrigenetics to be useful as a public health tool, there is a great need to use statistical and bioinformatics tools to examine the combined effects of multiple gene variants on health outcomes (76). While personalized nutrition based on genetics has great potential, there are many challenges in translating scientific advances into successful strategies for managing dietary intake and dietary health outcomes. These challenges include translating research results into practice, public perception and the likelihood of acceptance, issues of privacy and ethics, commercialization, and the level of evidence needed to enable a beneficial transition from traditional approaches (77).

## CONCLUSION

In this review, we explored preventative approaches to CVDs through nutrigenetics. Many genetic variants related to obesity and CVDs have been previously described. In our review, we concluded that genes encoding miRNA, APOB, PCSK-9, SORT1, cytokines, and IFN- $\gamma$  are strongly associated with CVDs the development and progression of CVDs. Mutations in these genes can cause serious morbidity and mortality. Therefore, genetic testing should be widely implemented, and familial predispositions should be considered when assessing an individual's health plan. With the help of nutrigenetics, we can determine the risk factors, identify preventative strategies, and improve the quality of life through personalized nutrition.

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# WHAT PHYSICIANS SHOULD KNOW ABOUT COFFEE

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## ABSTRACT

Coffee is one of the most frequently consumed non-alcoholic caffeine-containing beverages. For most physicians, specifically surgeons, morning coffee is considered an integral part of their daily routines. Caffeine is the most studied bioactive constituent of coffee. Coffee and caffeine have beneficial health effects on health, and it has been shown that coffee consumption can assuage the feeling of fatigue, improve alertness, decrease the risk of Alzheimer's disease, induce ergogenic effects, and may be protective against some types of cancer. On the contrary, too much coffee consumption came with side effects, such as tachycardia, increased blood pressure, and decreased bone density. However, most researchers agreed that coffee's benefits outweigh its downsides. In this review, several facts related to coffee consumption will be discussed, including its history, composition distribution, possible physiological effects, ways of serving, and the suggested daily consumption.

**Keywords:** Coffee, caffeine, physicians

## INTRODUCTION

The sound of the grinding machine, the coffee aroma smell, and the first sip of the morning cup; most coffee lovers start their day with these rituals; owing to its brain alerting effect, coffee has been thought to be a force in scientific development (1). This review aims to provide some insight related to coffee consumption by discussing factors related to coffee history, consumption, composition, possible beneficial physiological effects, ways of serving, and the suggested daily consumption.

## HISTORICAL PERSPECTIVE

The word coffee is believed to originate from an Arabic word, "qahwah," which refers to a particular type of wine and its dark color (2). For at least more than a thousand years, coffee has occupied a very important place in human society. Origins of consumption of coffee probably start from Northeast Africa, which then spread out to the Middle East in the 15<sup>th</sup> century and from there to Europe; there is some evidence that it was an established drink in the Yemeni Sufi monasteries,

from where it spread to other areas (3). Leonhart Rauwolff, a German physician, was the first European to remark coffee, around 1582, on his return from Mesopotamia searching for herbal treatments. He described it as "A perfect drink that is as black as ink and very good in illness, especially of the stomach." (4).

## COFFEE CONSUMPTION AMONG VARIOUS NATIONS AND MEDICAL PROFESSIONS

Coffee is considered one of the most used pharmacologically active non-alcoholic beverages, with its consumption becoming part of regular daily practices of modern life worldwide (1). However, coffee consumption varies among nations; Finland and Norway reported the highest consumption with a mean of 9.6 kg and 7.2 kg of coffee consumed per person per year, respectively, while consumption in the United States of America was reported as 3.1 kg per person per year (5). A Canadian Community Health Survey study reported that coffee comes in second place, the first being water, as the most popular drink among Canadian



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adults (6). The National Diet and Nutrition Survey in the United Kingdom demonstrated that a British adult consumes a mean of 130 mg of caffeine per day (7). In contrast, a Japanese adult consumes about 260 mg of caffeine per day (8).

For medical professions, it is generally accepted that surgeons consume more coffee than internists; in a Swiss center retrospective study by Giesinger et al. (4) evaluating coffee consumption of physicians at work and comparing the rate among different specialties (n=766 doctors), they found that 84% of physicians purchased coffee at least from one of the hospital canteens. Male physicians purchased significantly more cups of coffee per person each year than females (128±140 versus 86±86, p<0.01). Specialty had a significant effect on yearly coffee purchasing (p<0.01), where orthopedic surgeons reported the highest coffee purchase per person per year (89±136) followed by radiologists (177±191) and general surgeons (167±138), while anesthesiologists reported being the least (39±48). Interestingly, the hierarchical position significantly affected the pattern of purchasing (p=0.04), where senior consultants purchased most cups of coffee per person per year (140±169) while junior doctors purchased the least (95±85) (4). In a study by Do et al. (9) carried out on 271 Scandinavian anesthesiologists, the authors found that 91.3% of anesthesiologists were coffee drinkers, with a median of four cups daily. In a study by Tsigas et al. (10), the authors evaluated and compared the health behaviors between three groups, namely police officers, healthcare workers (doctors and nurses), and ambulance workers in Thessaloniki, Greece. The authors found that doctors reported the highest coffee consumption with a mean of 2.26±1.64 times per day, followed by nurses who reported consuming coffee 2.02±1.33 times per day (10).

## THE MAIN COMPONENTS OF COFFEE

Coffee is composed of a mixture of compounds, with caffeine being the most famous constituent (1). However, coffee is rich in various bioactive substances, which possess a variety of physiological effects. Up to 1,000 phytochemicals were described, including chlorogenic acid, lactones, theophylline, cafestol, niacin, vitamin B3, magnesium, and potassium (11). Caffeine was isolated from coffee beans as early as 1820, and since then, it has been the most investigated component of coffee for its pharmacological potentials and possible clinical applications (12). The amount of caffeine in a cup of coffee is determined by several factors, including first the type of coffee bean, and second the method of preparation. The two most widespread plant species that produce coffee beans are *Coffea arabica* and *Coffea canephora*. Researchers found that *Coffea canephora* contains about twice as much caffeine as

*Coffea arabica*: 68.6-81.6 versus 34.1-38.5 mg of caffeine per kilogram of dry coffee, respectively (13). The preparation method consists of a number of different variables, brewing water temperature, length of contact time, extraction pressure, bean grind size, and coffee bean roasting method (14). Therefore, while a home-prepared filtered coffee cup contains from 30 to 175 mg of caffeine, one espresso shot contains about 200-300 mg caffeine (15).

## THE PHARMACOLOGICAL EFFECTS OF COFFEE COMPONENTS

After ingestion of coffee, caffeine is absorbed totally in the small intestine in less than one hour, which then diffuses to other tissues (16). Caffeine has a half-life of approximately four to six hours and is metabolized mainly in the liver. Two to three cups of coffee could raise caffeine plasma levels to 20-40 mol/L; this concentration enables the main action of caffeine as an antagonist of adenosine, which is an endogenous inhibitory neuromodulator leading to drowsiness, fatigue, and sleep (17). As adenosine receptors are present in most tissues, such as the cardiovascular system (CVS), the central nervous system (CNS), liver, muscles, and adipose tissue, what is considered as the physiological effect of coffee is achieved through the blocking action of caffeine on adenosine receptors (14). Another action of coffee is its very potent antioxidant effect exerted through its primary polyphenol content: chlorogenic acid (18).

## EFFECTS OF COFFEE ON HEALTH

Generally, coffee, and its most important content caffeine, is the most used stimulant worldwide, owing to its safety and availability, as studies showed that coffee consumption was generally safe, often associated with more benefit than harm (19). Habitual consumption of coffee has several health benefits, which are shown by epidemiological data: it decreases the risk of neurological diseases (e.g., Parkinson's and Alzheimer's disease) and the development of certain cancers (e.g., hepatocellular, colorectal, and prostatic), as well as positively affecting liver functions and possibly playing a role in weight loss (its lipolytic effect increases metabolic rate and enhances energy expenditure) (14, 20). Furthermore, in the meta-analysis by Poole et al. (19) analyzing 201 articles to evaluate the relationship between coffee consumption and health outcomes, they found that consuming three to four cups of coffee per day is beneficial. They showed an association between coffee consumption and reduction in mortality, cardiovascular diseases, as well as neurological and metabolic conditions. In the following sections coffee's effect on various body systems is explained.

### Psychological and Central Nervous System

Caffeine has a CNS stimulant effect as it crosses the blood-brain barrier. It acts as an adenosine receptor antagonist; furthermore, it reduces the loss of dopamine and synergizes with noradrenaline, resulting in fatigue sensation reduction and a stimulated perception (21). Some studies showed that caffeine is an effective stimulant for enhancing simple measures of cognitive performance such as alertness and psycho-motor functions even after prolonged periods of sleep deprivation up to 85 hours (22-24). Franke et al. (25) investigated the use of coffee and its derivatives among surgeons, and after analyzing the responses of 951 surgeons they found that 66.8% reported habitually drinking coffee, and the most common reason for consuming caffeine was to reduce fatigue (54.3%), followed by to stay awake working night shifts (32.2%). A study on surgery trainees by Aggarwal et al. (26) was done using a virtual reality laparoscopic simulator to investigate the effect of caffeine on improving fatigue, as well as technical and neurocognitive skills. Eighteen participants were sleep-deprived and given 150 mg of caffeine on one occasion, and a placebo on another occasion, before performing the simulation laparoscopy. The authors found that after caffeine ingestion, the participants could restore the psychomotor skills to baseline and had a better reaction time compared to the placebo; however, the number of errors between both groups was same.

Coffee consumption was reported to have a protective effect against the development of Parkinson's disease in men and women (27). Moreover, the risk of Alzheimer's and Parkinson's diseases is less in regular coffee consumers (28, 29). Interestingly, a study reported that the relative risk of suicide was decreased by 13% for every cup of coffee consumed daily (29). Some recent studies have concluded a weak protective effect of coffee consumption on the risk of stroke; however, this is still yet to be proven (14).

### Endurance Performance and Physical Activity

It has been estimated that about 74% of elite athletes usually use caffeine as an ergogenic aid before or during sports, and endurance sports have the highest prevalence rate for caffeine consumption (30). A study showed that acute caffeine ingestion significantly affects endurance performance in the form of an increase in mean power output and faster time-trial times compared to placebo (31).

In a double-blind, randomized study by Church et al. (32) where the authors examined the ergogenic benefits of Turkish coffee taken an hour before exercise, the authors tested performance in a five km time trial, upper and lower body reaction to visual stimuli after ingestion of either 3.0 mg caffeine per kg body weight or decaffeinated coffee; they

found that the plasma concentration of caffeine, upper body reaction performance, respiratory exchange rate, and systolic blood pressure, were significantly higher with the Turkish coffee compared to the decaffeinated coffee. They concluded that ingestion of Turkish coffee resulted in better performance and improvement in reaction time and an increase in the feeling of energy. A meta-analysis of randomized controlled trials concluded that caffeine intake lowered the incidence of physical exertion during exercise, leading to longer exercise time (33). Furthermore, caffeine ingestion before prolonged cycling helped reduce muscle pain after exercise (34).

### Cardiovascular System

There is an ongoing controversy regarding the exact effect on the CVS; some suggest that coffee consumption has some adverse effects on serum cholesterol, blood pressure, and plasma homocysteine, whereas others suggest that the effect of caffeine within the coffee on epinephrine concentrations, hyperglycemia, and blood pressure seems to be weaker compared to caffeine taken in isolation (14, 20). Acute effects of coffee on the CVS presented as tachycardia, increased blood pressure, and occasional arrhythmia could occur directly after coffee intake; however, these are more profound in susceptible individuals (14). In a study by Bodar et al. (35) evaluating the effect of coffee consumption on atrial fibrillation (AF) development risk including 18,960 United States male physicians having a mean age of 66.1 years, the authors found a lower risk to develop AF among physicians who consumed one to three cups per day.

The association between coffee consumption and higher concentrations of total serum cholesterol and low-density lipoprotein cholesterol was attributed to the diterpene content in coffee oil; however, these compounds are usually removed by paper filters, so consuming filtered coffee may slightly increase serum cholesterol (36). The suggested harmful caffeine effect on the CVS may be neutralized by the benefits offered by other compounds in coffee; the 2015-2020 dietary guidelines for Americans associate the consumption of three to five cups of coffee per day with reduced risk for cardiovascular diseases (37, 38).

### Digestive System

Coffee consumption has a protective effect on the liver, helping to prevent the development and progression of liver diseases such as liver cirrhosis and hepatocellular carcinoma (39). This was explained by coffee's ability to lower the levels of liver enzymes (e.g., alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase) (39). Furthermore, studies have proven no significant relationship between coffee consumption and gastric ulcers, duodenal ulcers, and reflux esophagitis (40).



### Endocrine System

Studies have shown that the risk of developing type 2 diabetes decreases with regular coffee consumption (41). This protective effect was estimated to be dose dependent, with a 7% reduction in risk for each additional cup of coffee (41). In contrast, some studies have shown that caffeine alone can lead to impaired glucose tolerance (14, 20). However, this effect was also found in decaffeinated coffee, leading researchers to think that even if caffeinated coffee causes a hyperglycemic response (14, 20). Other bioactive compounds such as chlorogenic acids and phenolic compounds can neutralize this effect by altering glucose absorption, liver glucose metabolism, and insulin sensitivity (14, 20).

### Bone Metabolism

Heavy coffee intake has been associated with increased bone deterioration, lower bone density and the likelihood of fractures (14, 20, 40). This effect is due to the decrease in the efficiency of calcium absorption in the gastrointestinal tract caused by caffeine. This led dietitians to recommend calcium and vitamin D intake along with limiting coffee intake to 2-3 cups per day to reduce the risk of osteoporosis and related fractures, specifically in older age (42).

### Risk of Cancer

Generally, coffee consumption was associated with a lower risk of different cancers, including those of the liver and colorectum; however, no clear explanation was offered to explain the mechanism (14). It was suggested that caffeine acts as an anti-cancer compound by inhibiting extracellular signal-regulated kinases and  $\alpha$ -serine/threonine kinases and suppressing matrix-2 metalloproteinase and the  $\alpha$ -transforming growth factor of cancer-associated fibroblasts (43).

### Mortality

Some studies showed a statistically significant inverse association between coffee consumption and mortality after acute myocardial infarction (44). Compared with non-coffee drinkers, light (1-2 cups per day) and heavy (>2 cups per day) coffee drinkers had a decreased risk of mortality, with the maximum benefit being shown with heavy consumption (44).

## DOES COFFEE HAVE SIDE EFFECTS?

Although caffeine is considered safe, some side effects with its increased use have been reported with variation among subjects according to their metabolism rate, weight, age, and sex (45). These side effects might include tachycardia, jitteriness, agitation, headache, excitability, insomnia, and gastrointestinal tract symptoms, and symptoms of intoxication were reported to occur at a dose of 1,000 mg of

caffeine; doses of 3,000 to 10,000 mg might be lethal (46).

Furthermore, caffeine is known for its addictive properties, with a persistent desire to consume caffeine-containing foods or drinks and the possibility of developing withdrawal symptoms when caffeine ingestion is abruptly discontinued (20). Although the matter of being an addictive substance is debatable, some reviews showed that some of the symptoms necessary to diagnose dependency, mainly withdrawal symptoms (headache, fatigue, drowsiness), had been reported in heavy caffeine consumers after stopping intake (47). The explanation behind the appearance of some withdrawal symptoms is that with regular caffeine intake, the adenosine receptor numbers in the CNS increase, which makes individuals more sensitive to adenosine, and with subsequent reduction in caffeine consumption this will potentiate the usual physiological effects of adenosine, resulting in withdrawal symptoms (47).

## HOW IS COFFEE PREPARED AND BEST SERVED?

Generally, coffee is prepared by infusing hot water through the roasted and ground coffee beans. Various methods could be used, such as filtration, percolation, or pressure (39). It could be prepared through various methods: First-Brewed coffee (filter coffee) can be prepared simply by brewing ground coffee beans in hot water and then passing that through a filter to separate the grounds from the brewed coffee. A cup of 8-oz (237 mL) brewed coffee could contain up to 95 to 330 mg of caffeine (45). Second- Cold brew coffee (different from iced coffee) can be prepared by steeping the coffee grounds in water at room temperature between 8 and 24 hours and then served with ice in it (48). A 12-oz (355 mL) cold brew coffee cup could contain approximately 195 mg of caffeine (49). Third- Instant coffee can be prepared by adding hot water to the granules or coffee powder. It usually has less caffeine compared to freshly brewed coffee. An 8-oz cup of regular instant coffee contains about 30 to 70 mg of caffeine (45). Fourth- Espresso is prepared by forcing hot water or steam through very fine coffee grounds using a machine, stovetop mocha pot, or ready prepared capsules. A single serving of espresso contains about 50 to 150 mg of caffeine (45).

Some research reported that adding sugar to coffee contributes as a risk factor for health problems such as obesity and diabetes, so to keep the health benefits of coffee, adding sugar or sweetener is better avoided (50, 51). Studies showed that people who do not add sugar or sweeteners to their coffee had a lower risk of developing depression or metabolic syndrome (52, 53).



## HOW MUCH COFFEE SHOULD WE DRINK?

Moderate daily caffeine intake (about 2 to 4 coffee cups or 300 mg caffeine per day) is generally safe with less CVS stimulatory effects or behavioral changes in a healthy adult, leading to the natural beneficial effects (54). Dyslipidemic individuals might consume filter coffee, as the filters partly retain the main cholesterol-raising compounds in coffee such as cafestol and kahweol (45). People with known high blood pressure or cardiac arrhythmias are advised to limit caffeine intake; while for women planning on getting pregnant, it is better to limit their intake of caffeine to <300 mg per day (55). Besides, the people at risk of osteoporosis could add two tablespoons of milk to their coffee, which could neutralize the amount of calcium lost per one cup of coffee (55).

## CONCLUSION

Coffee is considered the most consumed beverage worldwide, and it contains various bioactive compounds, with caffeine being the most known and studied component. Coffee consumption is various among nations as well as among various medical specialties, with surgeons and senior consultants ranking as the highest consumers. The health benefits of habitual coffee consumption outweigh its harmful effects. Improving fatigue resistance and alertness, having positive effects on psychomotor functions, reducing Parkinson's risk, protecting against type 2 diabetes, and boosting physical activity were among the health benefits of coffee consumption. However, tachycardia, increase in blood pressure, and withdrawal symptoms were among its side effects. Coffee could be served through various methods: espresso, brewed, instant; and is better served without sugar. It is accepted that two to four cups of coffee per day is generally safe.

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# EFFECTS OF MALNUTRITION ON THE PROGNOSIS OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS

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## ABSTRACT

Acute lymphoblastic leukemia is the most common cancer among children and adolescents, with a rate of 34% of all cancers in this population. Studies have been conducted to question the relationship between the prognosis and nutritional status of pediatric acute lymphoblastic leukemia patients. Malnutrition refers to inadequate nourishment and obesity. Both ends of the spectrum of nutritional status might have implications on the prognoses. This review aims to illustrate the relationship between malnutrition and the acute lymphoblastic leukemia prognosis, and to address the bone health of the patients.

**Keywords:** Lymphoblastic leukemia, malnutrition, osteonecrosis

## INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer among children and adolescents, with a rate of 34% of all cancers in this population (1, 2). ALL is a malignant transformation and proliferation of lymphoid progenitor cells (3). Chromosomal abnormalities and genetic changes are the prognostic indicators of the disease (3). The incidence of ALL in children between newborn and 14 years of age is 3-4/100,000 and 1/100,000 in patients older than 15 years (2). The peak incidence age for ALL is 2 to 5 years of age (2). The clinical manifestation of ALL is the accumulation of poorly differentiated lymphoid cells in the bone marrow, peripheral blood, and extramedullary regions (3).

Dose-intensification strategies have improved the prognostic outcome in children between 1-14 years with ALL (4).

There have been studies that question the relevance of nutritional status on pediatric ALL patients' prognoses. The term 'malnutrition' generally connotes inadequate

nourishment, although, in clinical practice, it also refers to obesity (5). Both ends of the spectrum of nutritional status, under and over-nutrition, may have consequences on the prognoses. In this review, we aim to illustrate the relationship between malnutrition and the course of ALL.

Diagnosis of malnutrition is mainly based on standard anthropometric indices such as height-for-age or length-for-age Z-score and weight-for-length Z-score, mid-upper arm circumference (MUAC), and edema (6). If a child aged 6-59 months has at least one of either weight-for-height Z-score <-2, MUAC <125 mm or the presence of nutritional edema, he/she can be diagnosed with acute malnutrition (6). Another research aiming to provide consensus-based criteria for the diagnosis of malnutrition suggests two options (7). The first of these options is having a body mass index (BMI) lower than 18.5 kg/m<sup>2</sup>, and the second one is having unintentional weight loss and at least one of either low fat-free mass index or reduced BMI (<18.5 kg/m<sup>2</sup>) (7).



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### Symptoms of Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia usually has a variety of nonspecific symptoms (8). Fever caused by leukemia or a secondary infection due to neutropenia is one of these symptoms (2). Shortness of breath due to mediastinum enlargement, bone and joint pain, swelling of lymph nodes, fatigue and lethargy caused by anemia, petechiae and bleeding diathesis connected to thrombocytopenia are also different symptoms of ALL (2, 8).

### Relevance of Malnutrition with Clinical Outcomes for Patients with Acute Lymphoblastic Leukemia

Eighty-five percent of all children reside in developing countries, and the well-being of the community is adversely affected by the lack of accessibility to health care, presence of infectious diseases, or undernourishment (9). In developing countries, the prevalence of malnourishment in children under five years old is thought to be between 20% and 71% with an estimate of 43% (9). It is assumed that malnutrition is prevalent in 50% of pediatric cancer patients at diagnosis in the developing world, and in less than 10% in industrialized countries for ALL patients, which rises to 50% for patients with advanced neuroblastoma (9). Despite its value, data relevant to the nutritional aspect of cancer patients' presentations is lacking, especially in developing countries.

Evaluating the nutritional status of patients with malignancies at the time of diagnosis and tracking it during treatment is crucial due to its potential effect on disease progression and course of survival (9).

### Nutritional Morbidity at Diagnosis

In a study conducted with 105 Mexican ALL patients, no evidence of malnutrition was found, as measured by measurements of MUAC and triceps skinfold thickness (TSFT) for three months (10). Another Italian study compared 173 children, newly diagnosed with ALL, to 307 children with non-malignant diseases in terms of anthropometric measures; MUAC and TSFT (11). No statistically significant difference was observed ( $p=0.077$ ). Studies conducted in Casablanca and Guatemala revealed 20-50% of child patients who were being treated for cancer were malnourished (12, 13). However, a study ran in Northern Mexico pointed out that most pediatric ALL patients were well nourished when diagnosed (14). Another study, by Children's Cancer Group, that concentrated on obesity presentation in accordance with the patients' BMI assessed over 4,000 children and youths with ALL (15). They observed that the event-free survival rate for 5-years was worse in obese patients, with a higher possibility of relapse in patients at and over 10 years of age (15).

Due to these contradictory findings, the presence and prevalence of malnutrition at diagnosing ALL are inconclusive. However, most studies indicate that malnutrition may not be a prevalent problem at the time of ALL diagnosis (12, 14). The need for further assessment to determine the patients' risk of nutritional morbidity perseveres (12, 13).

### Nutritional Morbidity During Treatment

Some researchers believe malnourished patients have decreased tolerance to chemotherapy, altered metabolism for antineoplastic drugs, reduced immunity, are more prone to acquiring more persistent and common infections, and present a higher rate of therapy failure (16, 17).

Lobato-Mendizábal et al. (16) reported that malnourished children had a worse 5-year event-free survival rate (26%) than well-nourished children (83%). They also reported malnourished children had lower cumulative doses of maintenance chemotherapy and had more recurrences (16).

Another group reported that malnourished children, based on weight-for-height analysis, had a significantly higher risk of death in earlier phases of treatment compared to their well-nourished counterparts, the study also concluded that malnourished children were 3.5 times more likely to die during maintenance chemotherapy (17).

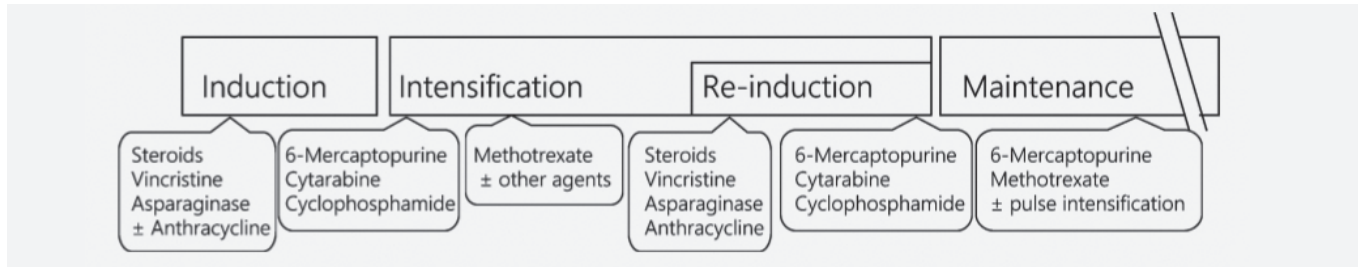
Cancer treatment may deepen nutrient deficiencies and cause nutritional morbidity, which shows a necessity for nutritional intervention (16, 17).

### Nutritional Status and Appetite-regulating Hormones in the Early Treatment of Acute Lymphoblastic Leukemia

The treatment of ALL aims to achieve normal hematopoiesis, to prevent resistant subclone formation and disease progression to other sites in the body, and to prevent relapse (10). Several treatment modalities differ from each other with the drugs involved in the protocol, but the main object of the treatment protocols depends on a basic strategy (10). Induction, consolidation, and maintenance is the most common three-phase treatment plan. Induction therapy aims to re-establish normal blood cell synthesis (10). The consolidation stage involves using agents to eradicate residual abnormal blood cells (10). These two stages can be considered as early treatment, whereas maintenance therapy aims to prevent relapse (18). Figure 1 shows common agents used in the three-phase treatment processes (8).

In addition to these therapeutic agents, environmental factors like diet and adequate nourishment are crucial for ALL treatment, especially during the early treatment stages since inadequate nutrition can decrease patients' tolerance to chemotherapy and cause reduced immunity, which increases susceptibility to infections and reduces survival





**Figure 1:** Treatment plan for pediatric acute lymphoblastic leukemia, taken from Kato and Manabe (8).

(19). In addition to this, dietary intake is known to contribute to ALL patients' bone health and mass, and certain dietary changes can contribute to the treatment-related toxicity in ALL patients (20).

Food intake is regulated by appetite-regulating hormones such as ghrelin, leptin, insulin, glucagon, and cortisol (21). However, appetite-regulating mechanisms are more complex in pediatric cancer patients (21). Increases and decreases in these hormones can manifest themselves with either weight gain or weight loss during and after ALL treatment, causing patients to be overweight or underweight, both affecting disease progression (21). However, there is no direct correlation between food intake and body composition in pediatric ALL patients, showing the complexity of the energy balance mechanisms involved in cancer (21). This complexity shows that there is a need for early intervention in the dietary status of ALL patients during early treatment stages to decrease the risk of nutritional complications (21).

It is common for newly diagnosed ALL patients to present in an underweight anorexic-cachectic state or an overweight state (22). For example, Brinksma et al. (22) showed that many newly diagnosed ALL patients had lower than predicted Z-scores in growth curves; whereas Ladas et al. (20) showed that 27% of newly diagnosed ALL patients were obese prior to treatment. Similarly, Gomes et al. (21) and Tan et al. (23) showed the percentage to be 21.4% and 24.5%, respectively. In addition, Lindemulder et al. (24) reported that many newly diagnosed pediatric ALL patients' BMIs statistically significantly increased between induction and consolidation treatments.

Studies showed varying results regarding levels of appetite hormones during treatment for ALL. Gomes et al. (21) showed a slight increase in ghrelin levels with no significant change in leptin levels. Park et al. (25) showed decreased leptin levels in pediatric cancer patients compared with healthy patients, whereas Moschovi et al. (26) showed no significant change in leptin levels throughout early treatment. Fasting insulin levels in the study conducted by Esbenshade et al. (27) showed a statistically significant increase during the first year of treatment, including maintenance therapy.

A better understanding of the complex appetite regulation mechanisms in the presence of cancer can lead to the development of more complex therapies for the disease progression of ALL and a better quality of life for ALL patients.

On the other hand, ALL is not the sole malignancy that may cause malnourishment in children (28). In patients with solid tumors, two studies reported the prevalence rate of malnutrition at diagnosis for neuroblastoma to be around 50% (28, 29). One study marked a decrease of 33% in malnutrition in neuroblastoma patients during treatment and 20% after the excision of the tumor (28). Another study reported a 31% malnourishment rate for patients with brain cancer which are medulloblastoma and supratentorial primitive neuroectodermal tumors (30).

These results indicate that malnutrition is a common problem for many childhood cancers along with ALL, and should be handled with care in order to improve the nutritional status of the patients and their quality of life.

### **The Importance of Malnutrition on Acute Lymphoblastic Leukemia and Bone Health**

Musculoskeletal system deformities are frequently observed in children and adolescents with ALL as the disease and its treatment itself have many adverse effects on musculoskeletal health (31-33). Over the last few decades, the cure rate of ALL approached 90%, therefore minimizing the short-term and long-term side effects of ALL and the intensive treatment protocols for ALL on patients' physical functions gained importance (32, 34, 35). Reduced bone turnover, bone mineral density (BMD), bone formation, musculoskeletal pain, in addition to abnormalities in gait, fractures due to osteoporosis, and osteonecrosis (ON) have been reported at diagnosis and during treatment of ALL (32, 34, 36-38).

### **Bone Mineral Density and Body Composition**

BMD increases until the early thirties in healthy people, but patients with ALL tend to have decreased BMD due to the disease, its treatment, lack of physical activity, and insufficient nutrition (33). Glucocorticoids, especially dexamethasone, have a major role in treating ALL in children as it promotes lysis of leukemic cells; however, it also reduces bone formation

by inducing apoptosis of osteoblasts and osteocytes (32, 39). Low BMD in childhood may ensue osteoporotic fractures later in life (39). Research by Alos et al. (40) revealed that 16% of children with ALL had vertebral fractures one year after beginning ALL treatment. The leukemic process has also been linked with low bone turnover as the leukemic cells secrete osteoblast-inhibiting factors and parathyroid hormone-related peptides (39).

In an effort to minimize the effect of low BMD in ALL survivors later in life, patients are often provided nutritional counseling and supplementation, such as vitamin D and calcium. A study conducted by Kaste et al. (41) showed that these treatments did not significantly remediate the low BMD over a two-year period.

Unfortunately, few studies have been conducted on the effects of nutritional deficiencies on bone health in ALL patients and survivors. However, one study suggests that it is possible to prevent the bone health complications of ALL treatment when the patient follows a nutrient-dense diet (42).

#### Osteonecrosis

Osteonecrosis is one of the most common and significant sequelae of ALL treatment, causing serious pain, decreased mobility, and joint collapse and therefore reduces long-term survivors' life quality (43). Previous studies show various results on the prevalence (1.6-17.6%) and risk factors of ON presentation during or after the antileukemic treatment (41). A study conducted by Mattano et al. (44) between 1989 and 1995 revealed 9.3% of 1,409 children with ALL experienced ON within 3 years after diagnosis. Another study reported the prevalence of ON observed in patients undergoing intensive chemotherapy for ALL as 1.6% (45). These different outcomes may stem from different types (dexamethasone, prednisone) or dosages of glucocorticoids, adolescent age at diagnosis, or radiation exposure (46). Kadan-Lottick et al. (46) also confirmed that patients treated with dexamethasone were 30% more likely to develop ON than patients treated with prednisone.

## CONCLUSION

There have been several studies about the relationship between ALL prognosis and malnutrition. As it can be seen in this review, the results are quite diverse. There are many different methods for evaluating the nutritional status of the patients. The lack of a standardized method could be the reason of these contradictory results. The reason of the discrepancies between findings might also be due to the differences in sample sizes, cohort characteristics, and chemotherapeutic agents used in different studies. Larger

trials examining appetite-regulating hormone levels and ALL disease progression are needed for better comparison. Therefore, it is not correct to compare every study. Nutritional status should still be considered, as ALL requires long-term treatment and has implications for both patients' quality of life and survival rates.

Adequate nourishment is crucial especially during the early treatment stages since inadequate nutrition could decrease the tolerance to chemotherapy as well as reduced immunity, and has negative effects on hematopoiesis (22, 47). It can lead to impaired production of blood cells, causing leucopenia and anemia. Furthermore, severe protein malnutrition in newborns and infants is related to atrophy in bone marrow and thymus, immature T cell number in the periphery rises and CD4/CD8 ratio decreases (47). These effects of malnutrition can reduce the patient's immunity, which could make the patient more susceptible to infections affecting survival rate (47).

There is a growing understanding that malnutrition is complex and reflects a range of overlapping comorbidities that are not fully understood.

Patients with ALL have a high recovery rate even with chemotherapy alone, and these patients have a good chance of living a long, healthy life after treatment. Therefore, clinicians should be aware of the importance of nutritional status and focus on patients' quality of life during treatment.

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# PARTICIPATION OF CANNABINOID RECEPTORS IN ANTIPRURITIC ACTIVITY INDUCED BY SYSTEMIC DIPYRONE IN MICE

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## ABSTRACT

**Aims:** The cannabinoid system has been shown to contribute to the antinociceptive effects of nonsteroidal anti-inflammatory drugs. Considering the similar pathophysiological mechanisms underlying pain and itching, we aimed to observe whether dipyron has an antipruritic effect and whether cannabinoid receptors are involved in this effect.

**Methods:** In this project, we produced scratching behavior in BALB/c mice, intradermally administering the well-known pruritic agent compound 48/80. After observing the anti-scratching effect of dipyron with increasing doses, we administered AM-251 (1 mg/kg, intraperitoneal) and AM-630 (3 mg/kg, intraperitoneal) to determine whether the endocannabinoid system was associated with this effect of dipyron.

**Results:** Dipyron reduced scratching behavior at its highest dose used in this study (600 mg/kg); however, neither AM-251 nor AM-630 changed the antipruritic action of dipyron.

**Conclusion:** Our findings indicate that dipyron, at higher doses, attenuates compound 48/80-induced scratching behavior in mice. Cannabinoid receptors have been found not to be involved in the antipruritic effect of dipyron. Further experiments are required to delineate the mechanisms underlying this high-dose dipyron effect.

**Keywords:** AM-251, AM-630, dipyron, pruritus

## INTRODUCTION

Cannabinoids have been known to reduce pain for centuries; however, several reasons preclude their use as effective analgesics (1). These chemical compounds include synthetic cannabinoids, those found in the Cannabis plant (phytocannabinoids), and those distributed throughout the body (endocannabinoids) (1). All cannabinoids activate cannabinoid receptors (CB1 and CB2) and take place in many pathophysiological processes (1). CB1 receptors are distributed widely in the central nervous system and appear to play the predominant role in both the therapeutic and the

central adverse effects of these drugs (1). Despite a great deal of research, cannabinoids are only used in limited indications. Synthetic cannabinoids, dronabinol and nabilone, are used in the treatment of chemotherapy-associated emesis, and nabilone is also approved for anorexia associated with acquired immunodeficiency syndrome (1). Nabiximol ( $\Delta^9$ -tetrahydrocannabinol + cannabidiol) is recommended for use in neuropathy and spasticity associated with multiple sclerosis and cancer pain (2, 3). These cannabinoids are still alternatives in aforementioned indications and are approved only in some countries; however, numerous ongoing clinical



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trials seem to enhance their usage in different pathological conditions in addition to its use for pain reduction (2, 3).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of medicines used worldwide to reduce pain, fever, and inflammation (4). They block the cyclooxygenase enzymes (COX-1, COX-2) and inhibit the production of prostaglandins (4). Distinct from traditional NSAIDs, paracetamol and dipyrone appear not to act on peripheral COX enzymes; a recent research indicates that they do not have a direct significant effect on endocannabinoid levels in a rat's brain and spinal cord (4). Yet, there are previous studies indicating that both increases in endocannabinoid tonus and cannabinoid receptors are associated with the antinociceptive effects of paracetamol and dipyrone (5-7). The cannabinoid system has also been proposed to participate in antipyretic, anxiolytic, and anticonvulsive effects of these drugs, although there are contradictory data (7-10).

Pruritus, also known as itching, is an uncomfortable, irritating sensation that provokes the urge to scratch (11). It is the predominant symptom of many diseases and can affect the quality of life (11). Overall, pruritus and pain are two sensations showing many similarities, especially in pathological and chronic conditions (11, 12). Accordingly, similar to pain, involvement of the cannabinoid system in the development of pruritus and the probable therapeutic effect of cannabinoids in pruritic states have been suggested (13, 14). Cannabinoid agonists have been shown to attenuate histamine-induced responses, while rimonabant, CB1 receptor antagonist, induced scratching behavior (13, 14). Similarly, we presented that activation of cannabinoid receptors using the synthetic cannabinoid agonist WIN 55,212-2 and enhancing endocannabinoid tonus via blockade of endocannabinoid degrading enzymes, fatty acid amide hydrolase, and monoacylglycerol lipase exhibit dose-dependent antipruritic activity (15-17).

This study aims to examine whether dipyrone reduces itching behavior induced by compound 48/80 (C 48/80) and to observe whether cannabinoid receptors mediate dipyrone's effects in case of any antipruritic action.

## MATERIAL AND METHODS

### Animals & Ethics

In this study, male BALB/c mice (2-3 months) weighing 20-30 g were used (Center of the Laboratory Animals, Trakya University). All animals were housed in a light (12/12 h day/night cycles) and temperature-controlled ( $21 \pm 2$  °C) room where food and water were available *ad libitum*. A total of 48 mice were used in this study. Separate groups, each involving 6 mice were used for each set of experiments. The experiments

were conducted after approval of the local "Animal Care Ethics Committee" (protocol code: TÜHADYEK-2019/27, date: 25.10.2019). Moreover, during all procedures, the Ethical Committee of the International Association for the Study of Pain guidelines were followed strictly (18).

### Study Design

Itching behavior was evoked by intradermal injection of 100  $\mu\text{g}/50 \mu\text{L}$  of C 48/80 into the rostral part of the back of each mouse. Several scratches per second were accepted as one bout of scratching. These scratches were videotaped and counted for 30 minutes, beginning just after administering C 48/80. To examine the antipruritic effect of the drug, different doses of dipyrone [150, 300, 600 mg/kg, intraperitoneal (i.p.)] were tested. Subsequently, effects of the cannabinoid CB1 receptor antagonist AM-251 (1 mg/kg, i.p.) and the cannabinoid CB2 receptor antagonist AM-630 (3 mg/kg, i.p.) on the antipruritic activity of dipyrone were analyzed. Dipyrone was injected 30 minutes before C 48/80 administration, and cannabinoid receptor antagonists were administered 10 minutes before dipyrone.

### Drugs

Compounds 48/80 and AM-630 were supplied from Sigma-Aldrich (St Louis, MO, USA); AM-251 was obtained from Tocris (UK); and dipyrone was purchased from Cayman (Ann Arbor, MI, USA). C 48/80 and dipyrone were dissolved in physiological saline, while AM-251 and AM-630 were administered in 20% dimethyl sulfoxide, 1% Tween 80, 1% ethanol, and 78% saline. Doses of each drug and treatment schedules were chosen from our previous studies (19-24).

### Statistical Analysis

Graphpad Prism 8.4 was used for statistical analysis and to plot the graphs. To assess the significance of any difference between groups, the Kruskal-Wallis test, then Dunn's Multiple Comparisons test were performed. In all analyses,  $p < 0.05$  was considered statistically significant.

## RESULTS

### Reduction of Compound 48/80-induced Scratching Behavior by Dipyrone

Dipyrone (150, 300, 600 mg/kg) administration attenuated C 48/80-induced scratches at its highest dose (30 mg/kg;  $*p < 0.001$ , compared to vehicle); but treatment with lower dipyrone doses had no effect on scratching behavior (Figure 1).

### Influence of Cannabinoid Receptor Antagonism on Dipyrone-induced Antipruritic Activity

Neither AM-251 (1 mg/kg) nor AM-630 (3 mg/kg) had any influence on the antipruritic activity of dipyrone (Figure 2).

### Effect of Cannabinoid Receptor Antagonists on Compound 48/80-induced Scratching Behavior When Administered Alone

When administered alone, AM-251 (1 mg/kg) had no effect on C 48/80-induced scratching activity whereas AM-630 (3 mg/kg) reduced C 48/80-induced scratches ( $*p < 0.001$ , compared to the vehicle; Figure 3).

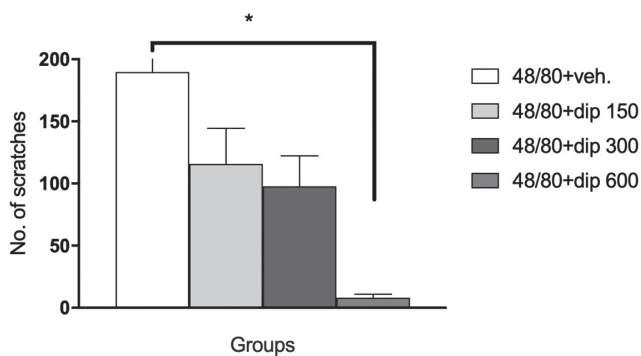
## DISCUSSION

Dipyrone is one of the most extensively used non-opioid analgesic drugs (25). Unlike traditional NSAIDs it has low anti-inflammatory activity but exerts substantial analgesic efficacy (25). It has been suspected for a long time that the central nervous system plays role in the antinociceptive effect of dipyrone and the contribution of the endocannabinoid system is one of the topics attracting attention to explain its mechanism of action (25). In this study, we investigated whether dipyrone produced antipruritic effects in mice who developed scratching behavior following C 48/80

administration and observed the contribution of cannabinoid receptors to its antipruritic action. In this study, dipyrone was found to be alleviating scratching at higher doses, but blockade of cannabinoid receptors was not found to be changing this effect.

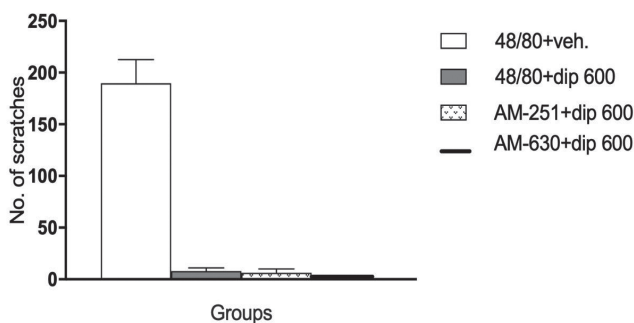
There are studies indicating that cannabinoid agonists and drugs elevating endocannabinoid tonus locally exert antipruritic effects (13-17). However, only a very limited number of studies have been conducted on the effects of NSAIDs, the non-opioid analgesic dipyrone and paracetamol, on pruritus. Systemic administration of two classical NSAIDs, tenoxicam and diclofenac, significantly reduced the incidence and severity of postoperative pruritus in patients receiving epidural opioids (26, 27). Moreover, paracetamol has been shown to reduce scratching behavior, especially at higher doses, but antagonism of CB1 and CB2 receptors have been shown not to prevent the antipruritic effects of systemic paracetamol (28-30). Similar to observations on paracetamol studies, our results indicate that dipyrone elicited antipruritic effects at the highest dose. Since many analgesic drugs dose-dependently blocked serotonin and C 48/80-induced scratching behaviors, with some exhibiting complete inhibition at certain doses, further experiments are needed to discriminate whether our findings will be evaluated as false-positive responses or not (29).

In this study, to clarify the mechanism of systemic dipyrone's antipruritic effect, the cannabinoid receptors were antagonized with AM-251 and AM-630. We observed that cannabinoid receptor antagonists had no influence on the anti-scratching effect of dipyrone, signaling that mechanisms other than the cannabinoid receptors are mediating its antipruritic action. In addition to COX inhibition, the classical mechanism of NSAIDs' effects such as the release of endogenous opioids, participation of nociceptin/orphanin FQ receptors, L-arginine/NO/cGMP/ $K_{ATP}$ , and/or the glutamatergic systems are among the suggested mechanisms for the peripheral and central



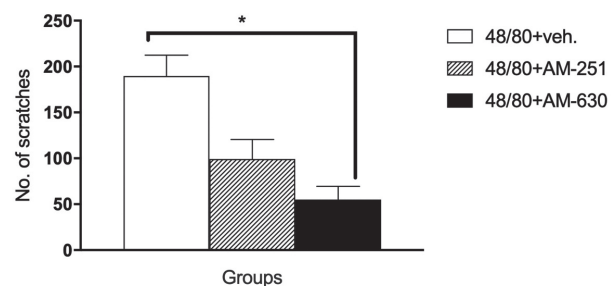
**Figure 1:** Effects of dipyrone (150, 300, 600 mg/kg, i.p.) on compound 48/80-induced scratches ( $*p < 0.001$ , compared to vehicle).

veh.: Vehicle, dip: Dipyrone



**Figure 2:** Effects of the cannabinoid CB1 receptor antagonist AM-251 (1 mg/kg, i.p.) and the cannabinoid CB2 receptor antagonist AM-630 (3 mg/kg, i.p.) on the antipruritic activity of dipyrone (600 mg/kg, i.p.).

veh.: Vehicle, dip: Dipyrone



**Figure 3:** Effects of the cannabinoid CB1 receptor antagonist AM-251 (1 mg/kg, i.p.) and the cannabinoid CB2 receptor antagonist AM-630 (3 mg/kg, i.p.) on compound 48/80-induced scratches when administered alone ( $*p < 0.001$ , compared to the vehicle).

veh.: Vehicle, dip: Dipyrone



antinociceptive effects of dipyrone (21, 31-35). Similar to its antinociceptive activity, all of these mechanisms may also mediate the antipruritic action of dipyrone, but detailed experiments on this area should be conducted.

Another interesting finding of our study was that the CB2 receptor antagonist AM-630 had no effect on the antipruritic effect of dipyrone but unexpectedly exerted anti-scratching properties when administered alone. Since CB2 receptors are mainly expressed in the periphery and do not mediate the central effects of cannabinoids, this appears to be an exceptional result. In our earlier studies, we found that AM-630, when injected intrathecally, did not exert any effect on its own or altered the antinociceptive action of diclofenac (36, 37). When other pruritus models, different techniques, and/or different routes of administration are used, we hope to see similar results as AM-630 having no effect when administered alone.

## CONCLUSION

We observed that the non-opioid analgesic drug dipyrone reduces C 48/80-induced scratching behavior in mice when given systemically, but only when it is used at the highest dose. Blockade of cannabinoid receptors has not participated in this antipruritic activity of high-dose dipyrone.

**Ethics Committee Approval:** This work was approved by Trakya University Local Ethics Committee of Animal Experiments (protocol code: TÜHADYEK-2019/27, date: 25.10.2019).

**Informed Consent:** N/A

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

**Author Contributions:** Concept: K.D.A., A.U., Design: E.A., N.A.F., R.G., Ö.T.Ö., K.D.A., A.U., Supervision: K.D.A., A.U., Resources: K.D.A., A.U., Materials: E.A., N.A.F., R.G., Ö.T.Ö., K.D.A., A.U., Data Collection and/or Processing: E.A., N.A.F., R.G., Ö.T.Ö., K.D.A., A.U., Analysis and/or Interpretation: E.A., N.A.F., R.G., Ö.T.Ö., K.D.A., A.U., Literature Search: E.A., N.A.F., R.G., Ö.T.Ö., K.D.A., A.U., Writing Manuscript: K.D.A., A.U., Critical Review: E.A., N.A.F., R.G., Ö.T.Ö., K.D.A., A.U.

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# MUCINOUS ADENOCARCINOMA MIMICKING CRYPTOGENIC ORGANIZING PNEUMONIA: A CASE REPORT

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## ABSTRACT

Mucinous adenocarcinoma of the lung is a type of malignancy that originates from glands or gland-like structures in the lung and can mimic pneumonia forms on radiological images. Our case report aims to raise awareness about this radiological pattern. A 72-year-old male patient was applied to an external center with the complaint of cough with sputum and back pain. Computed tomography revealed a kind of consolidation in the lower right lung zone of the patient. The patient, whose consolidation progressed in the lower right zone of the lung, was diagnosed with cryptogenic organizing pneumonia, and then corticosteroids were started. His condition worsened and a biopsy was requested for further investigation. The biopsy revealed mucinous adenocarcinoma of the lung in the patient. Mucinous adenocarcinoma is a malignancy that can be misdiagnosed as organizing pneumonia due to the similarities in patterns between the radiological images. Therefore, differential diagnosis of adenocarcinoma should be considered in cases of organizing pneumonia.

**Keywords:** Neoplasms, pneumonia, mucinous adenocarcinoma

## INTRODUCTION

Lung cancer is one of the world's leading causes of death (1). Lung cancers are mostly divided into two main groups: small cell lung cancers in about 15% of all lung neoplasms and non-small cell lung cancers (NSCLCs) in about 85% of all lung neoplasms (2). Lung adenocarcinoma is the most common form among non-small cell cancers at about 50% of all NSCLCs (3). Adenocarcinoma is a malignancy that originates from glands or gland-like structures and can occur in many organs. Pneumonia is the inflammation of the distal lung structures. If the pneumonia is not resolved, it can lead to the organization of inflammatory exudate, which leads to fibrosis in the lung tissue, called organizing pneumonia. Organizing pneumonia is a prominent inflammatory lung disease due to easily reversible intra-alveolar fibrosis (4, 5).

Exclusion of any other etiology and a histopathologic examination of the lung tissue leads to the diagnosis of

"cryptogenic" organizing pneumonia (COP) while organizing pneumonia secondary to other conditions such as infectious agents, drugs (5-aminosalicylic acid, acebutolol, amiodarone, amphotericin B, bleomycin, busulfan, carbamazepine, cephalosporin, fluvastatin, gold salts, methotrexate, etc.), radiation, or malignancy termed as "secondary" organizing pneumonia (5). Lung adenocarcinoma is known to mimic different types of pneumonia, including organizing pneumonia, and can be confused on computed tomography (CT) imaging (6).

In this study, we aimed to present a patient whose pneumonia mimicked COP, who was later diagnosed with mucinous adenocarcinoma after his condition worsened. As it can be difficult to distinguish between these two pathologies, we believe that this study will raise awareness about the differential diagnosis of these conditions.



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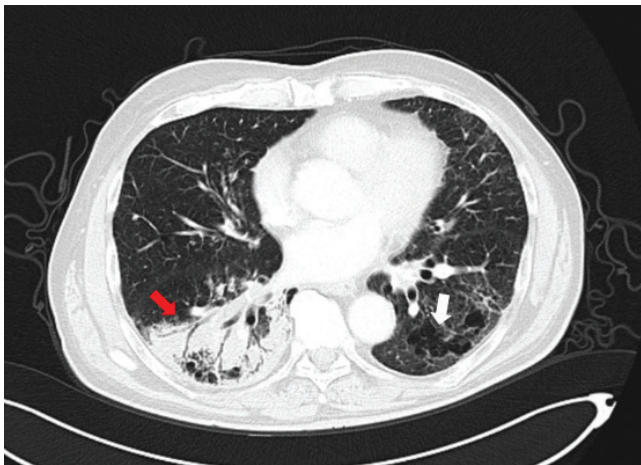


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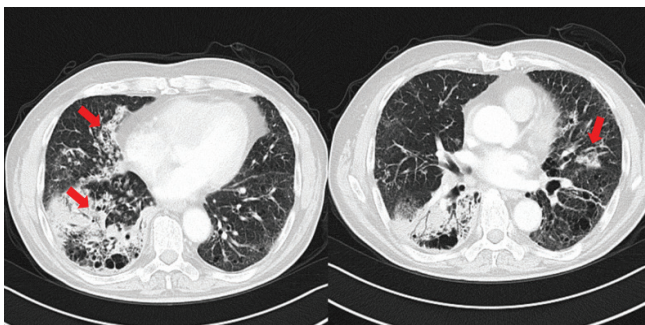
## CASE REPORT

A 72-year-old male patient applied to an external center with complaints of cough with sputum and back pain. The patient was a retired metal worker with a 40-year smoking history and had quit smoking for 12 years. The patient had no chronic disease other than hypothyroidism.

A CT scan was performed on the patient (Figure 1), and the patient who was diagnosed with community-acquired pneumonia was referred to Trakya University School of Medicine Hospital, Department of Chest Diseases for further examination. The chest CT performed on the patient showed pneumonic infiltrates that progressed in the right lower lobe (Figure 2). Flexible bronchoscopy was requested to find the cause of pneumonia. According to the results of bronchoscopy, no signs of infection or endobronchial lesion were found. The basal segment openings of the lung were edematous and bronchoalveolar lavage from the right lower



**Figure 1:** A homogeneous consolidation area with air bronchogram is observed in the posterobasal segment of the lower lobe of the right lung (red arrow). In addition, cystic emphysematous changes are observed in the lower lobe of the left lung (white arrow).



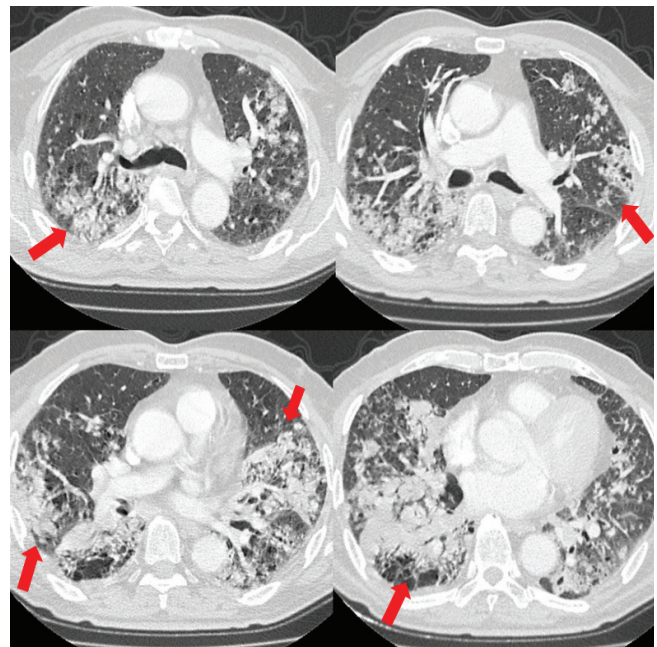
**Figure 2:** Axial plane contrast computed tomography scan 6 weeks after the first admission. In addition to previous consolidations in the lower right basal segment, newly developed air bronchograms and consolidation areas are observed in both lungs (red arrows).

lobe revealed inflammation, but no malignancy was found. In addition, a sample was taken for bronchoalveolar lavage culture.

The patient was then recalled with the results of the lavage culture. The patient did not have chest pain or hemoptysis, but sputum and dyspnea continued. Inspiratory sounds were coarse, and crackles were heard in the lower zone of the right lung. Saturation of peripheral oxygen ( $SpO_2$ ) levels were normal. No bacterial growth was detected in the bronchoalveolar lavage culture, and a contrast-enhanced CT scan was requested.

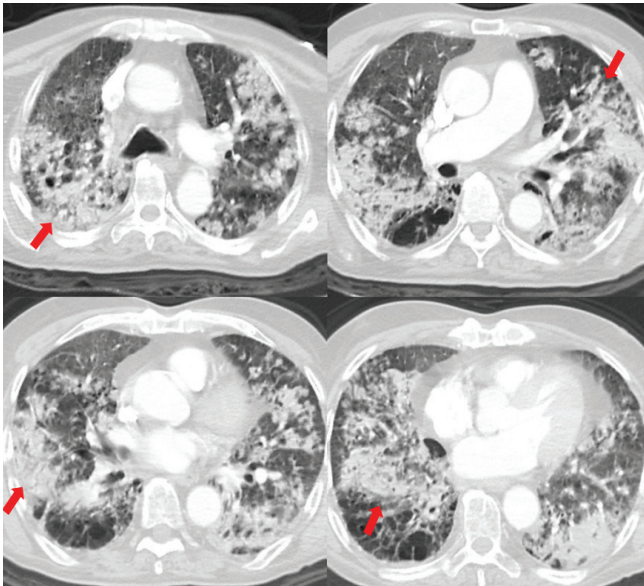
Computed tomography findings (Figure 3) were evaluated as COP due to the absence of other etiological factors. The patient was started on methylprednisolone (40 mg/day) and levofloxacin (750 mg/day) for two weeks. No disease progression or improvement in his condition was observed in this period, and the patient started to suffer from severe dyspnea. The patient was hypoxic with  $SpO_2$  levels between 65-70%. The patient was given oxygen supplementation and was started on piperacillin-tazobactam for two weeks. Chest CT was also requested. Both lungs had peripheral consolidations compared to older CT scans (Figure 4). The patient also had a negative coronavirus disease-2019 polymerase chain reaction test in this period.

The patient was then referred to the department of interventional radiology for percutaneous transthoracic lung

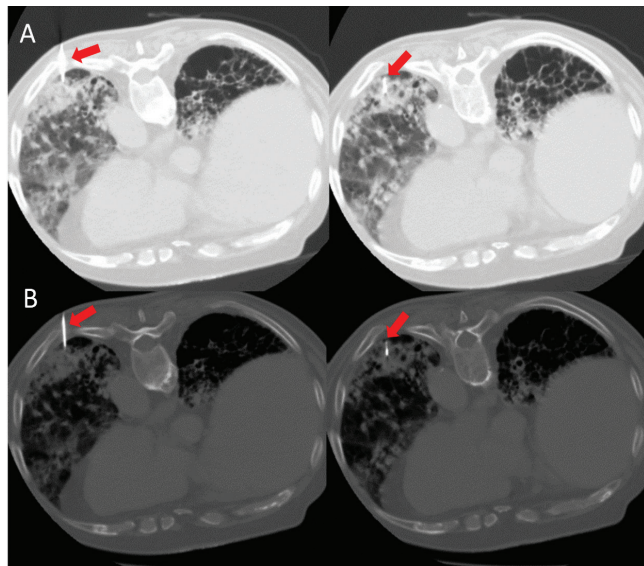


**Figure 3:** Axial plane contrast computed tomography scan, 5 months after the first admission. The increasing number of infiltration areas are observed in both lungs (red arrows). Infiltration areas consist of nodular consolidation that tends to coalesce.





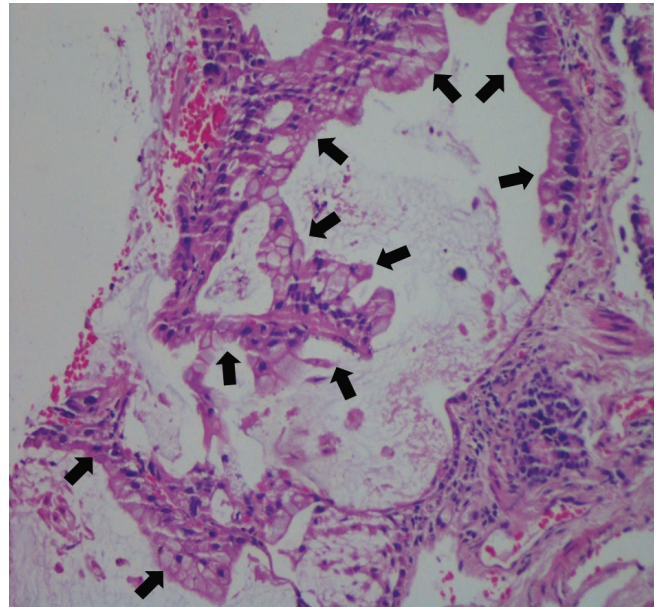
**Figure 4:** Axial plane contrast computed tomography scan, 7 months after the first admission. Increasing infiltration areas are observed in both lungs. Infiltration areas consist of common consolidation areas (red arrows).



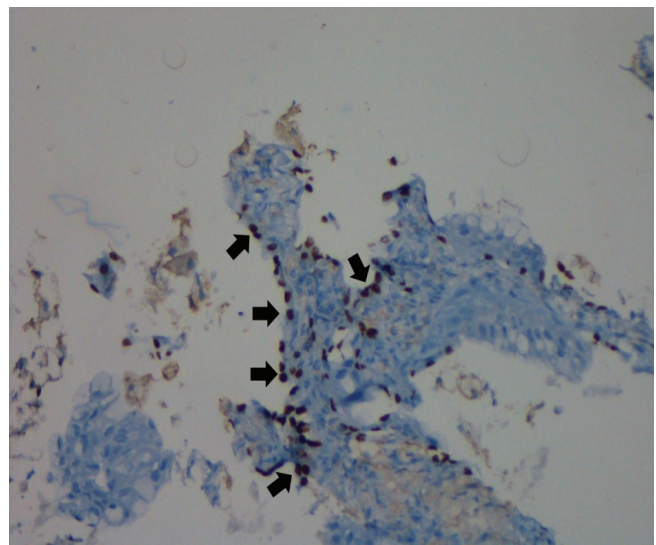
**Figure 5:** Core needle biopsy was performed by entering percutaneous from the consolidation area observed in the lower lobe of the left lung (red arrows). A: Lung parenchyma window. B: Bone window.

biopsy (Figure 5). Biopsy material was positive for thyroid transcription factor-1 and negative for P40 stains, confirming the diagnosis of lung adenocarcinoma (Figure 6, 7).

Adenocarcinoma was determined as mucinous type with lepidic pattern [World Health Organization (WHO) classification of bronchoalveolar carcinoma pre-2011]. Although a definite classification of invasiveness could not be made on the small biopsy material after diagnosis, the



**Figure 6:** Cubic and columnar tumor cells with a basally located nucleus and abundant cytoplasmic mucin lining the alveolar wall (arrows) (hematoxylin & eosin stain, x100 magnification).



**Figure 7:** Positive stain for thyroid transcription factor-1 antibody in pneumocyte nuclei (arrows) (x100 magnification).

patient was referred to the department of medical oncology for chemotherapy.

**DISCUSSION**

Cancer is among the deadliest diseases with approximately 10 million deaths worldwide (7). According to studies conducted by WHO, lung cancer ranks first in the list with 1.8 million deaths in 2020 (7).

Adenocarcinoma is the most common histological subtype of lung cancer, and many different subtypes are depending on the mucinous differentiation and invasion stage (3). In our case, the patient had mucinous adenocarcinoma with a possible lepidic predominant pattern.

World Health Organization 2011 classification removed the term of bronchoalveolar carcinoma and added subtypes of adenocarcinoma *in situ*, minimally invasive adenocarcinoma, invasive mucinous adenocarcinoma, and lepidic-predominant invasive non-mucinous adenocarcinoma (6). Organizing pneumonia CT patterns include peripheric patchy consolidations, ground-glass opacities, perilobular opacities, reversed halo sign, nodules, and masses (8). Consolidations and ground-glass opacities were found to be characteristics of both general lung adenocarcinoma (previously bronchoalveolar carcinoma) and organizing/infectious pneumonia, though the peripheral distribution of consolidation and nodular pattern were found to be significantly more common in patients with adenocarcinoma (8, 9). Findings of cysts, cavities, CT angiogram sign, and leafless tree bronchogram sign were not significantly different among pneumonia and adenocarcinoma (9).

Detterbeck et al. (10) described pneumonic type adenocarcinoma radiologically as regional rather than the nodular appearance of varying areas of ground glass and consolidation. Microscopically they are typically found to be mucinous adenocarcinomas that are invasive with a predominance of lepidic growth. The increasing prevalence of CT imaging made cancers with ground glass and/or lepidic nodules seen more commonly. Moderate levels of correlation have been reported between imaging and histological subtypes of these pneumonic-type adenocarcinomas. The consolidative pattern was around 33-75% of the cases. Areas of ground glass are observed in about 75% of the cases (10). The five-year disease-free survival rate for lepidic predominant adenocarcinoma was found to be around 72-90% (11).

In our case, we observed a similar progressive consolidation pattern on CT scans of the patient, and the peripheral consolidations suggested the diagnosis of lung adenocarcinoma. However, the absence of nodular pattern was more in favor of pneumonia. It can be confused with mucinous adenocarcinoma of the lung and COP due to similar radiological findings. Other diagnoses must be ruled out before a diagnosis of COP can be made.

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**Ethics Committee Approval:** N/A

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

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

**Author Contributions:** Concept: B.A., M.G.Ö., A.A., Design: B.A., M.G.Ö., A.A., Supervision: B.A., M.G.Ö., A.A., Resources: A.A., Materials: A.A., Data Collection and/or Processing: B.A., M.G.Ö., A.A., Analysis and/or Interpretation: B.A., M.G.Ö., A.A., Literature Search: B.A., M.G.Ö., A.A., Writing Manuscript: B.A., M.G.Ö., A.A., Critical Review: B.A., M.G.Ö., A.A.

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# SYNCHRONOUS GASTRIC AND COLON ADENOCARCINOMA WITH SIMULTANEOUS SURGERY: A CASE REPORT

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## ABSTRACT

Multiple primary tumors are rare but their incidence is increasing. We aimed to present a case report about a patient with synchronous gastric and colon cancer, who has undergone a simultaneous resection of both tumors and developed (preventable) postoperative complications. A 69-year-old male patient, who was diagnosed with severe acute respiratory syndrome coronavirus-2019 infection 3 months ahead of his admission, presented to the Trakya University due to gastric bleeding. Colonoscopy and esophago gastro duodenoscopy were performed upon complaints. The patient was diagnosed with synchronous gastric and colon adenocarcinoma. Total gastrectomy, left hemicolectomy, and Roux-en-Y esophagojejunostomy were performed simultaneously. Although there were no postoperative surgical complications, the patient developed a pulmonary embolism. In the presence of a gastrointestinal tumor, the synchronous or metachronous tumor should also be evaluated. The most appropriate surgical treatment is simultaneous resection of both tumors. Physicians should also consider the risk of a pulmonary embolism that may develop after these major surgeries.

**Keywords:** Synchronous neoplasms, gastric cancer, colon cancer, pulmonary embolism

## INTRODUCTION

Multiple primary tumors were first defined as developing tumors with different histological features, localized in different positions and self-metastasized more than once in the same patient (1). Later, in 1932, it was published for the first time in a study by Warren and Gates (2), which included 1,259 case reports, and highlighted the importance of these tumors.

The prevalence of multiple primary tumors in the current medical literature is between 0.73-11.7% (3). Its incidence varies between 2% and 17% (4). While gastric cancer is the fourth most common type of cancer in the world; it ranks fifth for men and sixth for women in Turkey (5). Colorectal cancer follows a similar trend and while it is the third most common type of cancer seen in men and second in women in the world; it is in third place for both sexes in Turkey (5).

Multiple primary tumors consist of two subclasses: synchronous and metachronous (6). If the second tumor is detected earlier than 6 months after the first tumor, it is synchronous; if it is detected later than 6 months, it is called metachronous (6). These definitions vary depending on the source. While the distinction between synchronous and metachronous is determined in the 2-month mark based on the Surveillance Epidemiology and End Results Program data, International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC) data suggest the 6-month mark (4, 7). European cancer registries commonly use IACR/IARC definitions in practice (4).

Examples of synchronous cancer combinations are esophagus and stomach, stomach and colon, stomach and duodenum. The combination of stomach and colon cancer is rare (8-10). Colorectal cancer is the most common synchronous cancer in patients with gastric cancer; on the other hand, the most



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common synchronous cancer in patients with colorectal cancer is gastric cancer (6, 11).

We aim to present a case report about a rare case of synchronous gastric and colon cancer. We believe this case will contribute to the literature with the treatments performed and prognosis on this rare condition.

## CASE REPORT

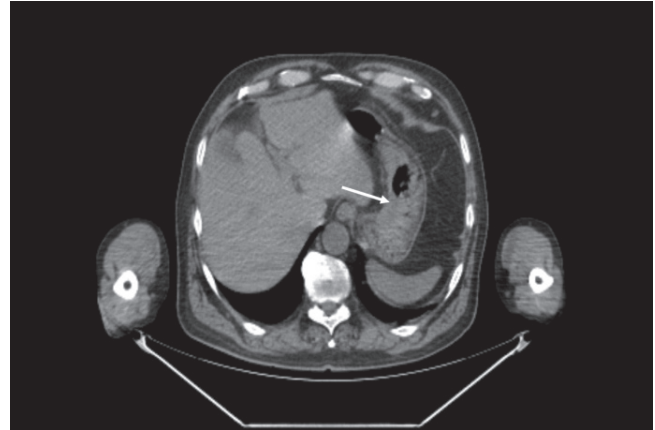
A 69-year-old male patient was admitted to the Trakya University Hospital with loss of consciousness due to gastric bleeding. No pathological finding was detected in the physical examination. The patient's family history revealed colon cancer in the patient's father. The patient had been diagnosed with severe acute respiratory syndrome coronavirus-2019 infection 3 months before presentation and had recovered since. The patient has a history of type 2 diabetes mellitus. The patient smokes 30 packs of cigarettes per year and does not consume alcohol. The patient has a history of angiography 3 years ago. The blood tests indicated the presence of anemia in the patient with a hemoglobin level of 9.6 g/dL.

Colonoscopy was performed on the patient and revealed an ulcerovegetan mass obstructing the lumen in the descending colon. An esophago-gastro-duodenoscopy was performed based on the patient's anemia. The esophagus and duodenum were found to be normal, and a malignant ulcer was found in the gastric fundus.

After the diagnosis of gastric cancer, positron emission tomography/computed tomography scan was performed for staging. Images suggested thickening in the abdominal wall and increased fluorodeoxyglucose (FDG) uptake in the stomach fundus and lesser curvature (Figure 1). Moreover, FDG uptake in the thickening area of the left colon wall was detected (Figure 2). No metastasis was detected in the imaging.

Biopsy from the colonoscopy report was evaluated as weak cohesive carcinoma infiltration in the stomach and adenocarcinoma in the colon. The patient was diagnosed with synchronous gastric and colon adenocarcinoma. Total gastrectomy, left hemicolectomy, and Roux-en-Y esophagojejunostomy were performed simultaneously.

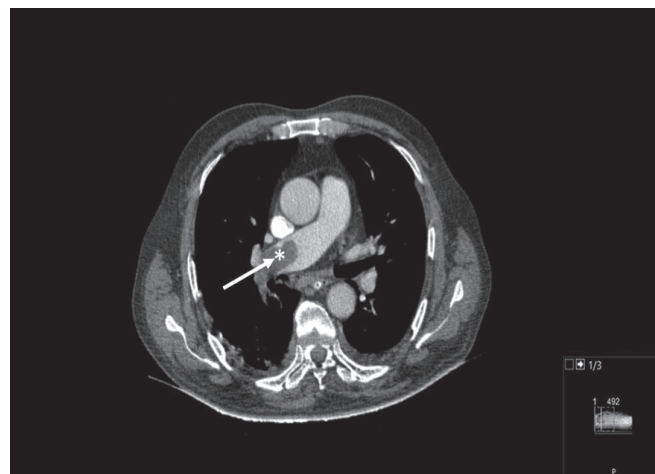
On postoperative day 3, a thrombus was detected in the right pulmonary artery in the patient despite anticoagulant treatment (Figure 3). The patient was diagnosed with pulmonary embolism and is still being followed up in the intensive care unit. No other postoperative surgical complications were observed. Patient was started on enteral nutrition.



**Figure 1:** Abdominal computed tomography imaging without contrast. Increased thickness and irregularity in the abdominal wall at the level of the lesser curvature of the stomach (arrow).



**Figure 2:** Abdominal computed tomography imaging without contrast. Increased tumoral wall thickness in the descending colon extending to the surrounding adipose tissues (arrow).



**Figure 3:** Contrast-enhanced thorax computed tomography scanning the pulmonary artery phase. Filling defect compatible with thromboembolism in the right main pulmonary artery (asterisk and arrow).

## DISCUSSION

The etiology of the synchronous cancer is still unknown (11). Risk factors include defects in DNA error repair mechanism, family history, male gender, and increasing age (over 50 years of age) (11-15). The generally accepted incidence of synchronous tumors associated with gastric cancer is 2.0-10.9% (16). Ławniczak et al. (17) stated an incidence of 6.7%, whereas Ha et al. (6) suggested 1% (18). With the development of screening techniques in recent years, there has been an increase in the diagnosis of synchronous tumors (16).

Incidence rates suggest that when the patient has gastric cancer, we should also consider the possibility of a synchronous tumor, especially colorectal cancer (19). Colonoscopy should be performed for colorectal cancer in patients presenting with bleeding and bowel obstruction (19). Since these complaints may not always be present, screening tests should be performed for patients presenting with a form of gastric cancer (19). Further investigations should be performed in the preoperative period in patients who have gastric cancer or are older than 50 years of age, male, have a family history of gastric cancer, and undergoing cancer treatment (19). In addition, the risk of metachronous tumors should be considered in the postoperative period.

The prognosis of the patients with multiple tumors is primarily determined by the progression of gastric cancer and therefore it is crucial to first operate on gastric cancer (6, 20). Moreover, if only colon surgery was performed, the patient would not be able to intake nutrients due to gastric cancer. However, if only gastric surgery had been performed, an anastomotic leakage could have occurred due to obstructive colon cancer. As a result, a simultaneous surgery should be preferred as the treatment method as presented in this case.

Pulmonary embolism is the most common preventable cause of hospital deaths (21). The development of pulmonary embolism depends on many factors such as type of surgery, preoperative prevention methods used, patient's age, and gender of the patient (22). Overall, any type of surgery increases the risk of pulmonary embolism five times compared to patients with no history of surgery (23, 24). About 25% of all pulmonary embolism cases can be associated with recent surgery (23). Pulmonary embolism is seen 1.4 times more frequently in men (21, 25). The rates also vary according to the operated body region and type of surgery (22, 23, 26). In a United States-based study, 65% of patients with pulmonary embolism had undergone surgery, and 41% of these patients had undergone general surgery (26). Moreover, the same study revealed that 82% of these patients had undergone open surgery, suggesting that open surgery as a major risk factor (26). The second most common

comorbidity was cancer, which was found in 22% of the patients. Anticoagulants were used in 56% of patients before postoperative embolism developed. The time between surgery and diagnosis of pulmonary is age-related and is 7 days above the age of 60 (26). The incidence of pulmonary embolism after major surgery varies by region and year. It was found to be 0.3-30% in a global review in Japan, 0.09% in a study conducted in the United States, and 11.8% in France (21, 23, 26).

Based on the patient's age, gender, cancer history, and the operation performed, the patient presented in this case was considered to have a higher risk of pulmonary embolism. The patient was put on compression stockings preoperatively and low molecular weight heparin was given as an anticoagulant. However, the patient still experienced a postoperative pulmonary embolism. The patient was transferred to the intensive care unit after the embolism and is still being followed up in the intensive care unit.

This presented case reflects the importance of evaluating synchronous or metachronous tumors in the presence of a gastrointestinal tumor. If there is another tumor present, the most appropriate surgical treatment is simultaneous resection of both tumors applied to the patient presented in this case. Finally, our case highlighted the importance of being extra vigilant for potential pulmonary embolism in higher-risk patients following multiple tumor surgeries.

**Ethics Committee Approval:** N/A

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

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

**Author Contributions:** Concept: M.Y.K., İ.E.C., Design: M.Y.K., İ.E.C., Supervision: M.Y.K., İ.E.C., Resources: M.Y.K., İ.E.C., Materials: M.Y.K., İ.E.C., Data Collection and/or Processing: M.Y.K., İ.E.C., Analysis and/or Interpretation: M.Y.K., İ.E.C., Literature Search: M.Y.K., İ.E.C., Writing Manuscript: M.Y.K., İ.E.C., Critical Review: M.Y.K., İ.E.C.

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# CORNEAL ENDOTHELIAL CELL ANALYSIS IN TWO PATIENTS WITH WILSON'S DISEASE AND KAYSER-FLEISCHER RINGS

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## ABSTRACT

We aimed to present two patients who were suffering from Wilson's disease along with the Kayser-Fleischer rings. Patient 1: A 15-year-old female patient was admitted to Trakya University School of Medicine Hospital with worsening consciousness, slurred speech, and cognitive impairment. The neurological examination was consistent with Wilson's disease. In the ophthalmologic examination, Kayser-Fleischer rings were revealed. Right corneal cell density was found to be 3270 cell/mm<sup>2</sup> and the left corneal endothelial cell density was found to be 3177 cell/mm<sup>2</sup>. Patient 2: A 12-year-old female patient was admitted to the Trakya University School of Medicine Hospital with complaints of difficulty in speaking, involuntary movements of her limbs, and inability to stand or sit. Additional symptoms were microphonia, episodic abnormal posture, and rigidity of the limbs. Corneal endothelial cell density was found to be 3287 cell/mm<sup>2</sup> in the right eye and 3720 cell/mm<sup>2</sup> in the left eye. The corneal copper deposition forming a Kayser-Fleischer ring caused no changes in endothelial cell morphology.

**Keywords:** Corneal endothelium, Kayser-Fleischer ring, microscopy, Wilson's disease

## INTRODUCTION

Wilson's disease is an autosomal recessive disorder of copper metabolism that results in the pathological accumulation of copper in many tissues, primarily the liver, brain, and cornea (1-3). This accumulation results in liver disease such as genetic hemochromatosis and iron overload disorders, and a-1 antitrypsin deficiency, as well as neurological symptoms, and Kayser-Fleischer (KF) rings (1). Although a KF ring is considered the pathognomonic sign of Wilson's disease, it is not confined to this disease. A KF ring can also rarely be found in the presence of chronic cholestatic disorders, such as primary biliary cholangitis and neonatal cholestasis (2, 3). A KF ring appears as golden-brown pigment deposits at the level of the Descemet's membrane of the corneal periphery (2, 3). It has been reported that KF rings may exist in the asymptomatic phase of the disease, furthermore, they may be a sign of disease severity, and their regression is possible with treatment (2-4). However, the effects of this copper

accumulation on the morphology of the endothelial cells are not known.

In this study, a noncontact specular microscope Topcon SP3000P by Topcon Cooperation in Tokyo, Japan was used for endothelial cell analysis. With this method, images of the corneal endothelial cells are taken by a photomicroscope and sent to a computer, which is used with a specular microscope, in order to perform image analysis by software.

The following parameters can be calculated with a specular image, using the instruments' built-in software: endothelial cell density, hexagonality, and coefficient of variances of the endothelial cell layer.

Endothelial cell density is the number of cells in the corneal endothelium per mm<sup>2</sup>. The mean value for adults is 2400 cells/mm<sup>2</sup> (1500-3500 cells/mm<sup>2</sup>). Endothelial cell density may decrease with age, in the presence of corneal diseases, after surgical procedures or trauma.



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The standard deviation of the mean cell area divided by the mean cell area gives the coefficient of variation, which is a unitless number normally less than 0.30.

The percentage of hexagonal cells with 6 apices should ideally approach 100%. Lower percentages indicate a diminishing state of health of the endothelium.

In this case report, we aim to present the corneal endothelial cell analyses of two Wilson's disease patients with KF rings.

## CASE REPORTS

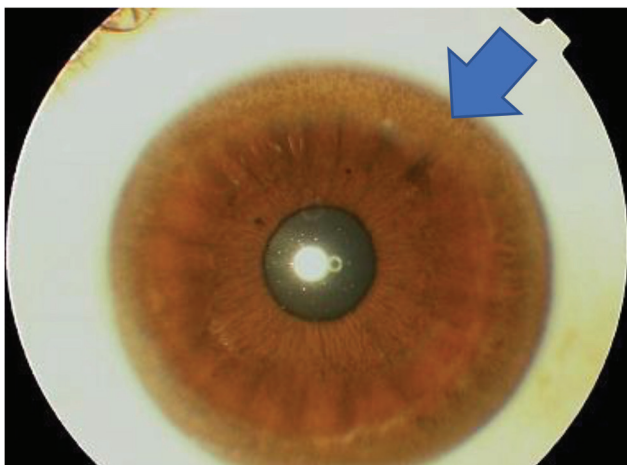
**Patient 1:** A 15-year-old female patient who exhibited increasingly worsening unconsciousness with slurred speech and cognitive impairment over the previous two weeks was admitted to Trakya University School of Medicine Hospital. Neurological examination showed emotional lability, motor impersistence, hypokinetic dysarthria, postural and intentional tremor affecting the upper extremities, and overall rigidity. Magnetic resonance imaging showed a symmetrical high signal intensity in the putamen, caudate nucleus, the posterior limb of the internal capsule, and parietal white matter on T2 weighted images, with no atrophic changes. Ophthalmic examination found the visual acuity to be 10/10 in both eyes. KF rings were observed in the stroma of both corneal peripheries with biomicroscope (Figure 1). Corneal endothelial cell analysis was performed with a noncontact specular microscope (Figure 2). The right corneal endothelial cell density was found to be 3270 cell/mm<sup>2</sup> and the left corneal endothelial cell density was 3177 cell/mm<sup>2</sup> (Table 1). The ophthalmoscopic examination was normal.

**Patient 2:** A 12-year-old female patient born to nonconsanguineous parents presented with a five-year history of dysarthria, a four-year history of involuntary movements of limbs, and a one-year history of an inability to stand or sit. The microphonia, which was initially present, progressed to aphonia afterwards. The patient also had a history of episodic

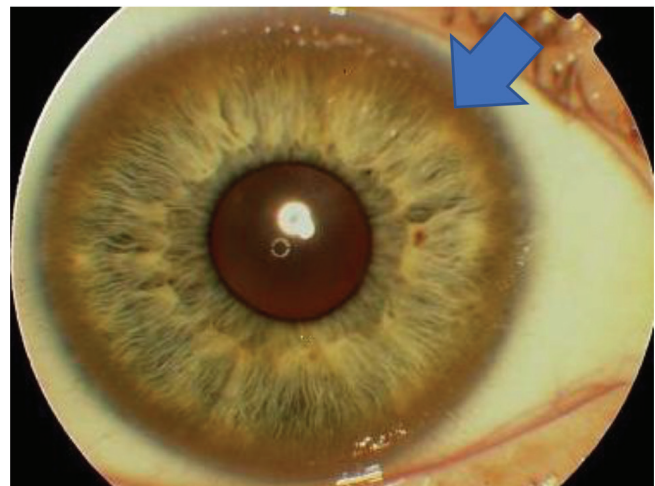
abnormal posturing and rigidity of limbs. There was no history of jaundice, convulsion, or autonomic disturbances. The ophthalmic evaluation revealed visual acuity to be 10/10 in both eyes. KF rings were observed in both corneas (Figure 3). Corneal endothelial analysis was performed with a noncontact specular microscope (Figure 4), and corneal endothelial cell density was found to be 3287 cell/mm<sup>2</sup> in the right eye and 3720 cell/mm<sup>2</sup> in the left eye (Table 1). No pathology was detected in the ophthalmoscopy.



**Figure 2:** Corneal endothelial cells of the right eye of patient 1 were imaged.



**Figure 1:** Slit-lamp image of the right eye of patient 1. Kayser-Fleischer ring is observed (shown with the arrow).



**Figure 3:** Slit-lamp image of the right eye of patient 2. Kayser-Fleischer ring is observed (shown with the arrow).

**Table 1: Results of the corneal endothelial cell analysis of the patients.**

Cases	Eye	Cell density (cell/mm <sup>2</sup> )	Coefficient of variances (n)	Hexagonality (%)
Case 1	Right	3270	25.6	77
	Left	3177	29.8	68
Case 2	Right	3287	27.5	79
	Left	3720	28.9	62



**Figure 4:** Corneal endothelial cells of the right eye of patient 2 were imaged.

## DISCUSSION

In this case report, corneal endothelial cell analysis results of two Wilson's disease patients with KF rings were found to be normal.

Although there is still much to discover about the pathogenesis of Wilson's disease, it is thought to either stem from a lack of serum ceruloplasmin synthesis or from an abnormal protein with a high affinity for copper that binds copper in the tissues (5). Copper deposits were found in the corneal stroma and on the anterior capsule of the lens. Clinically, deposition in the cornea results in a KF ring, while deposition in the anterior capsular lens results in a sunflower cataract. There are studies reporting a remission of both KF ring and sunflower cataract upon treatment of the disease (3). However, the clinical manifestations of corneal endothelium deficiency have not been reported in patients with a KF ring, and the endothelial morphology of these patients has not yet been studied.

Reactions caused by copper-containing intraocular foreign bodies are known as "ocular chalcosis". Since the intraocular

foreign body is usually intravitreal in these patients, toxic effects caused by copper were observed in the vitreous, retina, and lens, while no changes were observed in the cornea (5).

Findings from these patients show that eyes with KF rings have normal corneal endothelial cell morphology. This observation also leads to the conclusion that the accumulated copper does not cause a toxic or inflammatory effect. The fact that copper, which is known to have toxic effects, did not cause changes in corneas with KF rings can be explained by the fact that copper is protein-bound, and not free. Another possibility is that the abnormal protein, which is assumed to be present in Wilson's disease, may reduce the toxic effects of copper.

In conclusion, it was determined that the KF ring, which is the pathognomonic finding of Wilson's disease, did not cause a morphological change in the corneal endothelium. Longitudinal studies evaluating larger numbers of subjects are still needed to confirm these data.

**Ethics Committee Approval:** N/A

**Informed Consent:** Informed verbal consent was obtained from both patients.

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







**Author Contributions:** Concept: E.G., Design: V.G., Supervision: V.G., Resources: E.G., V.G., Materials: E.G., V.G., Data Collection and/or Processing: E.G., Analysis and/or Interpretation: E.G., Literature search: E.G., Writing Manuscript: E.G., Critical Review: E.G., V.G.

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# ADULT HEMISPHERIC PILOCYTIC ASTROCYTOMA WITH HEMORRHAGIC COMPONENTS: A CASE REPORT

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## ABSTRACT

We aim to present a 35-year-old male patient who was operated on for a left temporoparietal pilocytic astrocytoma with hemorrhagic components. We present a 35-year-old male patient with three months of pressure in the ear, pain in the neck, and swelling in the eyes. Cranial magnetic resonance imaging revealed a consistent mass with glial tumor morphology with cystic and hemorrhagic components in the left temporoparietal region. A gross-total excision was performed, and the pathological examination was consistent with pilocytic astrocytoma. The postoperative period was uneventful, and at the 3.5-year follow-up, the patient was free of any symptoms and radiological recurrence. Adult pilocytic astrocytomas with hemorrhagic components are relatively rare tumors. A gross-total resection, along with a close follow-up, is the primary treatment modality.

**Keywords:** Pilocytic astrocytoma, neurosurgery, headache, hemorrhage

## INTRODUCTION

Pilocytic astrocytoma (PA) is considered a grade I tumor in the World Health Organization classification, which denotes a slow-growing, non-malignant tumor and is a relatively common glioma that often presents with a cystic lesion (1, 2). It is most often located in the cerebellum but can occur in all parts of the central nervous system including the optic nerve, hypothalamus, cerebellum, brain stem, and spinal cord (1, 3). Neuroradiologically, PA mostly appears as a contrasted and well-defined mass (4).

Pilocytic astrocytoma is more common in younger age groups, and its incidence decreases with age. The 0-14 years of age range has a higher incidence than the 15-39 and 40+ years of age ranges (5). According to the statistical reports

from the Central Brain Tumor Registry of the United States, men are affected slightly more frequently than women, and incidence rates are highest among white patients compared to black, American Indian/Alaska Natives, and Asian/Pacific Islanders (5). In a study with 3,084 children from the United States, the incidence was reported 8,227 per million (6).

Headache is a common symptom for PA, yet visual disturbances, high intracranial pressure, hydrocephalus, vertigo, motor, and sensory deficits, psychiatric manifestations such as personality changes or mood-related symptoms, seizures, ataxia, and speech disturbances may also occur in PA patients (7, 8). However, a hemorrhagic onset is rare in PA patients, with 26 adult cases of hemorrhagic pilocytic astrocytoma (HPA) having been reported so far (9, 10).



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The origin of the hemorrhagic component in PA is unclear and controversial. However, White et al. (11) suggested that abnormal vascularity in PA, such as thick-walled hyalinized vessels, foci of vascular endothelial hyperplasia, and thin-walled ectatic vessels, may be associated with hemorrhage.

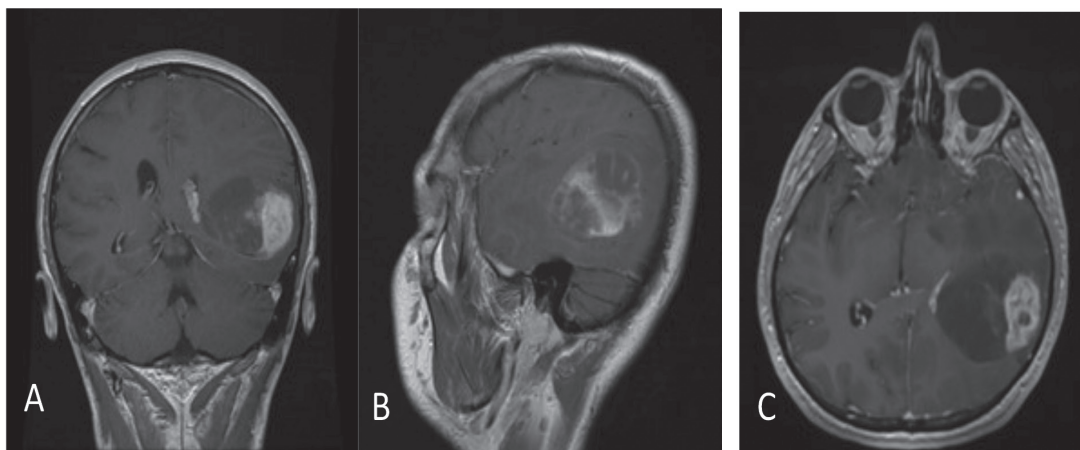
In this study, we aimed to present a 35-year-old male patient diagnosed with cerebral PA with a hemorrhagic component.

## CASE REPORT

A 35-year-old male patient was admitted to the Neurosurgery Department of Trakya University School of Medicine with complaints of pressure in the ear, neck pain, and swelling in the eye. The complaints had been going on for three months. The patient was a social drinker, a non-smoker, and his medical history was unremarkable. Cranial magnetic resonance imaging (MRI) showed a mass, consistent with glial tumor morphology, in the left temporoparietal region (Figure 1) and cystic and hemorrhagic components in some places (Figure 2).

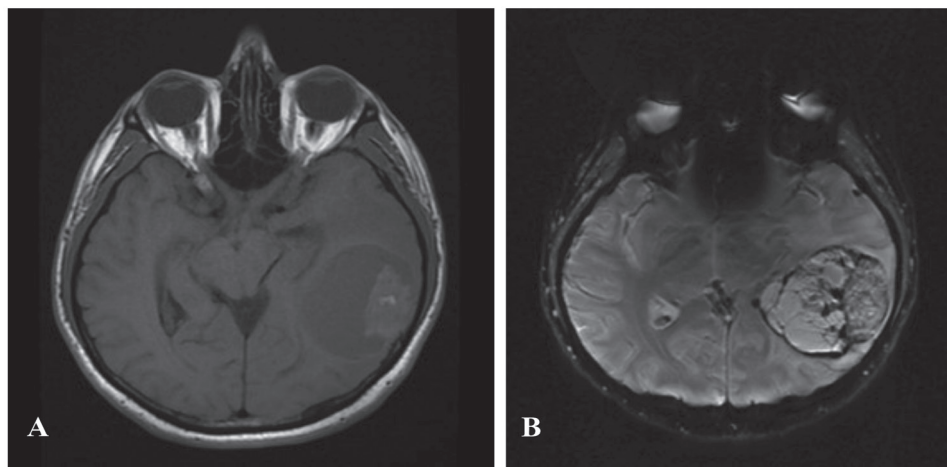
The preoperative contrast-enhanced MRI images revealed a lobule contoured mass in the left temporoparietal area, approximately 53x55x43 mm in size. The mass caused significant pressure on the occipital horn in the left lateral ventricle, resulting in a shift of approximately 1 cm in the midline and had peripheral diffuse vasogenic edema. It also included cystic, solid, and hemorrhagic components. After intravenous contrast agent injection, heterogeneous enhancement in the solid component and annular enhancement in the cystic component was prominent (Figure 1, 2). Recurrence was not noticed in the patient's early and late postoperative MRI images (Figure 3, 4).

Left temporoparietal craniotomy was performed under general anesthesia. First, the dura mater was cut and opened in a semilunar shape. Then, a trajectory was planned through a dirty yellow region of the cortex using the navigation system (S7 StealthStation, Medtronic, Minneapolis, Minnesota, USA). The biopsy sample was consistent with a glial tumor.



**Figure 1:** Preoperative contrast-enhanced T1-weighted MRI images. A: Coronal plane. B: Sagittal plane. C: Axial plane.

MRI: Magnetic resonance imaging



**Figure 2:** Preoperative axial imaging sequences. A: Non-contrast T1-weighted. B: Susceptibility weighted.



Subsequently, the tumor was removed completely (Figure 5). The sample was examined histologically (Figure 6).

No residual tumoral residue was observed in the early postoperative MRI (Figure 3).

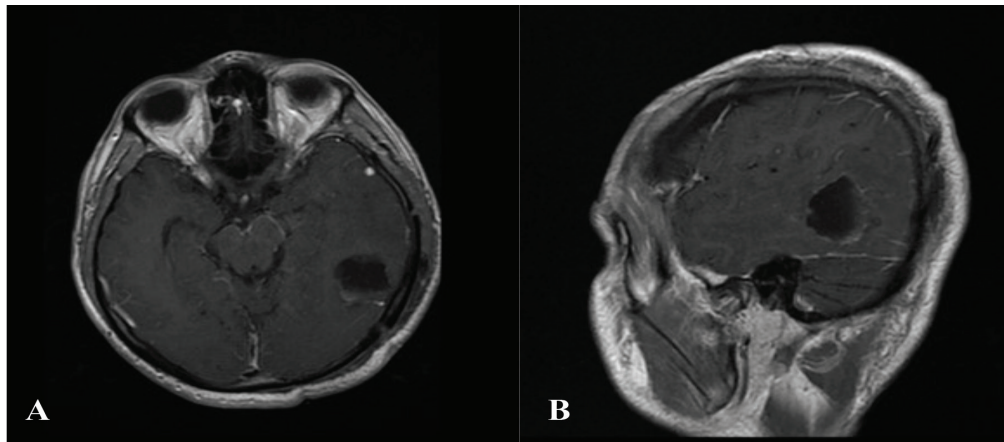
## DISCUSSION

The presented case of PA is notable for the patient's age, supratentorial location, and hemorrhagic components.

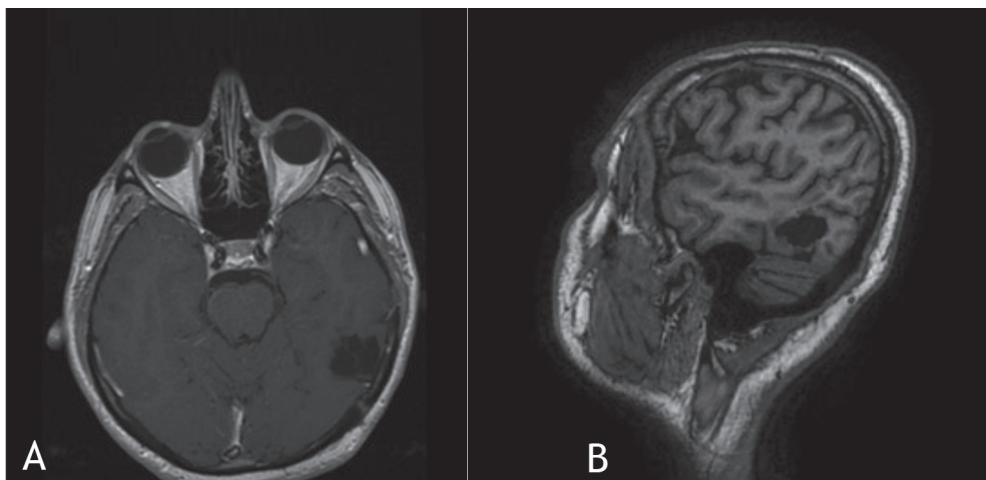
The possibility of postoperative morbidity with radical tumor resection is low in PA (12). The prognosis of patients after surgical intervention is excellent, with a 96% 5-year survival rate. An adjuvant radio or chemotherapy is unnecessary (13). In the 20-44 years of age group, the 5-year survival rate is 90.7% (5). The 25-year survival rate after resection is between 50-94% (3).

Our literature search revealed that there are 26 adult patients with HPA (9, 10). The male to female ratio was 2.1:1. Although PAs were mainly located in the cerebellum and the brainstem, HPAs were mainly located in the cerebral hemispheres, hypothalamus, suprasellar region, and cerebellum. Nine patients had HPA located in their cerebrum (10). In our patient, the tumor was located in the left temporoparietal region.

The most common symptom was a sudden headache accompanied by vomiting. Other common symptoms were vision problems, limb paresis, and seizures (10). Our patient had an unusual set of symptoms, such as pressure in the ear, pain in the nape, and swelling in the eyes. Rosenthal fibers allow us to separate these tumors from other astrocytic gliomas (14). In our case, Rosenthal fibers were also observed (Figure 6).



**Figure 3:** Early postoperative contrast-enhanced T1-weighted MRI images, one day after the operation. A: Axial plane. B: Sagittal plane. MRI: Magnetic resonance imaging



**Figure 4:** Late postoperative contrast-enhanced T1-weighted MRI images, approximately three and a half years after the operation. A: Axial plane. B: Sagittal plane.

MRI: Magnetic resonance imaging



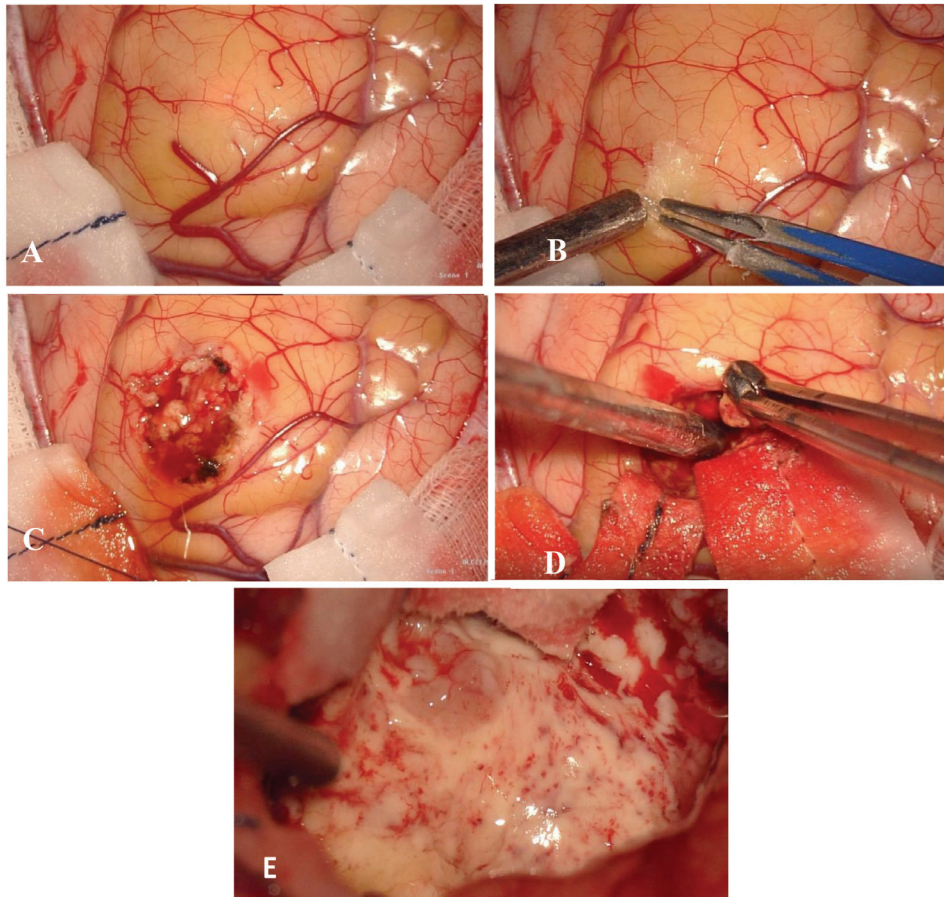


Figure 5: A-E: Perioperative images.

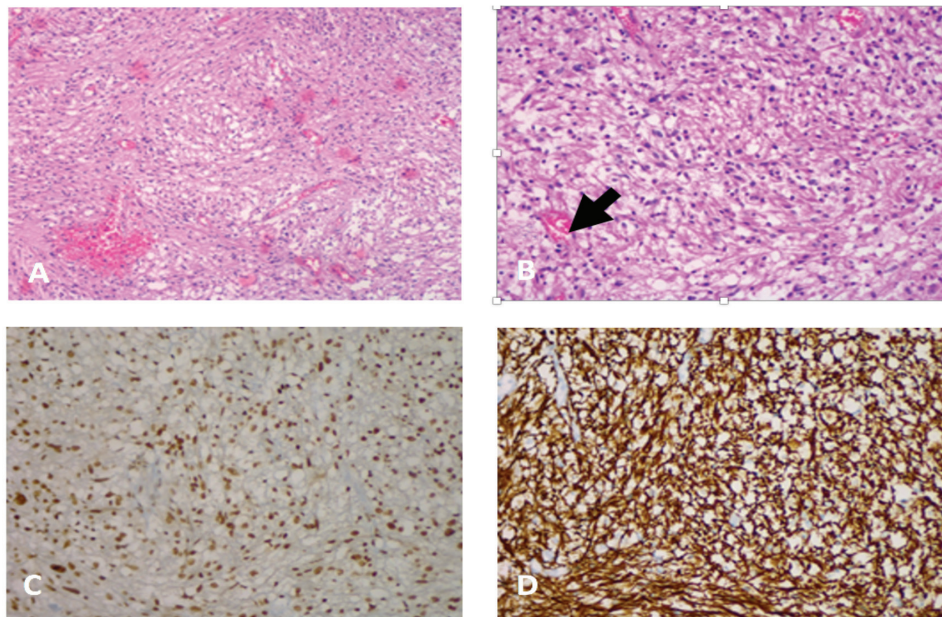


Figure 6: A: Small microcystic cavities and glial tumors containing increased vascular structures of different calibers (hematoxylin & eosin stain, x100 magnification). B: The neoplastic glial cells, pilocytic cells with long thin nuclei, protruding cytoplasm, and Rosenthal fiber which is shown with an arrow (hematoxylin & eosin stain, x200 magnification). C: Tumor diffuse nuclear reaction with ATRX (immunoperoxidase, x200 magnification). D: Diffuse cytoplasmic and fibrillary staining with GFAP (immunoperoxidase, x200 magnification).

There are various options for PA treatment such as subtotal resection, gross total resection, radiotherapy, adjuvant radiotherapy, and stereotactic radiosurgery (7). A gross-total resection is recommended whenever possible, as it has the best prognosis for this disease (12). PA is relatively rare in adults and is considered a potentially treatable glioma with gross total resection (15-17).

We presented a 35-year-old male patient with left temporoparietal PA with cystic and hemorrhagic components. A gross-total excision was performed, and the follow-up was uneventful. The patient had no complaints, and no radiological recurrence was present at the 3.5-year follow-up. A typical PA is seen in pediatric patients in the cerebellum with cystic components. However, it can also be seen in adults, in cerebral hemispheres with cystic and hemorrhagic components, as in this case. The prognosis is favorable after surgical resection. Therefore, a gross-total resection followed by a close follow-up is the treatment of choice.

**Ethics Committee Approval:** N/A

**Informed Consent:** Informed verbal consent was obtained from the patient for this study.

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

**Author Contributions:** Concept: Ö.P., N.C., A.E.Ç., E.M.D., B.C., A.T.A., Design: Ö.P., N.C., A.E.Ç., E.M.D., B.C., A.T.A., Supervision: Ö.P., N.C., A.E.Ç., E.M.D., B.C., A.T.A., Data Collection and/or Processing: Ö.P., N.C., A.E.Ç., E.M.D., B.C., A.T.A., Analysis and/or Interpretation: Ö.P., N.C., A.E.Ç., E.M.D., B.C., A.T.A., Literature Search: Ö.P., N.C., A.E.Ç., E.M.D., B.C., A.T.A., Writing Manuscript: Ö.P., N.C., A.E.Ç., E.M.D., B.C., A.T.A., Critical Review: Ö.P., N.C., A.E.Ç., E.M.D., B.C., A.T.A.

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# MITRAL VALVE INFECTIVE ENDOCARDITIS IN AN INTRAVENOUS DRUG ABUSER

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## ABSTRACT

Infective endocarditis is a disease characterized by endocardial surface infection of the heart with high mortality and morbidity. The infection mostly involves heart valves, defects, or permanent heart devices. The aim of this case is to present a young patient with mitral valve involvement and infective endocarditis who is an intravenous drug abuser. A 26-year-old male patient was admitted to the Trakya University School of Medicine Hospital Emergency Service with complaints of fever and shortness of breath lasting for 10 days. The patient had no medical history other than active smoking and intravenous drug use. On physical examination of the patient, an apical 2/6 systolic murmur was detected. Transthoracic echocardiography performed with the suspicion of infective endocarditis revealed a large mobile mass in the mitral valve. Transesophageal echocardiography was performed to confirm the diagnosis. This revealed an open foramen ovale pattern and moderate mitral regurgitation. Increased inflammatory parameters and positive blood cultures for *Staphylococcus aureus* were detected in the laboratory. The patient was operated on for mitral valve replacement with a definitive diagnosis of infective endocarditis. Infective endocarditis is a disease that can be difficult to diagnose because of its clinical presentations similar to other diseases. Therefore, infective endocarditis should be considered in the etiology of fever, unexplained worsening of general condition, and a newly developed heart murmur, especially in people using intravenous drugs.

**Keywords:** Infective endocarditis, intravenous substance abuse, mitral valve

## INTRODUCTION

Infective endocarditis (IE) is known as infection of natural or prosthetic heart valves, endocardium, or intracardiac devices caused by bacterial, viral, or fungal pathogens (1, 2). Up to 10 out of every 100,000 people are affected by IE each year (3). Despite advances in its management, IE has still been considered a disease with a high risk of morbidity and mortality, a 15-20% in-hospital mortality risk, and a one-year mortality rate of up to 40% (4). In recent years, changes have been observed in the epidemiology of IE due to the aging of the population, the increase in the number of people using intravenous drugs, and the use of artificial heart devices and heart valves (3).

The type of affected valve and the duration of the infection period are used to classify IE (4). The distinction between

natural and prosthetic valve endocarditis is important for clinical management. The period of the infection is classified as acute (few days-6 weeks), subacute (6 weeks-3 months), and chronic endocarditis (more than 3 months) according to the duration of infection and the time interval when signs and symptoms occur (5).

In this case report, we present an unusually located IE without any predisposing heart disease in a young intravenous (IV) drug abuser patient.

## CASE REPORT

A 26-year-old male patient with a history of active smoking and IV drug use, was admitted to the Trakya University Hospital emergency department with complaints of fever and shortness of breath lasting for 10 days. On physical



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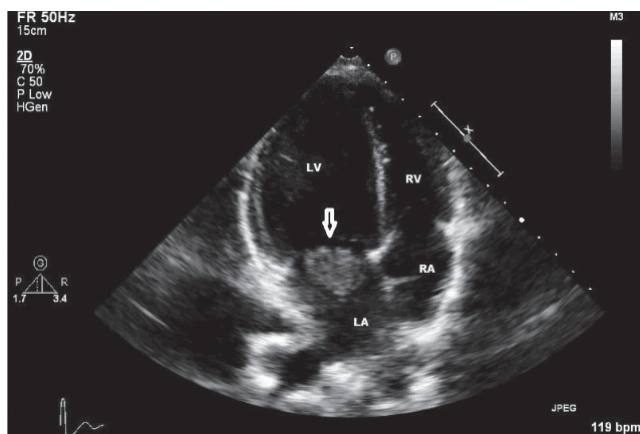
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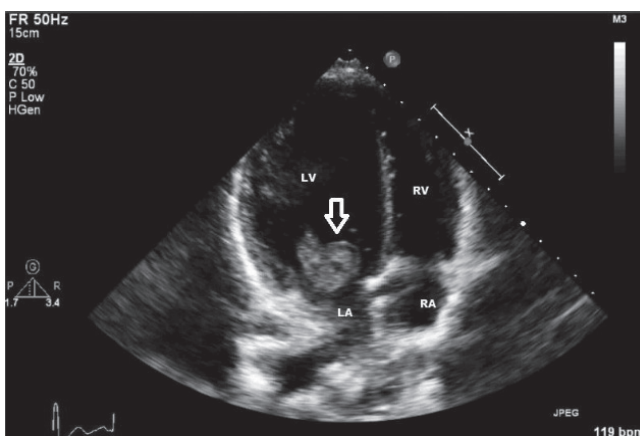


examination, body temperature was 39.1 °C, blood pressure was 110/60 mmHg, sinus tachycardia at a rate of 104 beats/min, and an apical 2/6 systolic murmur was found. Due to suspicion of IE, a transthoracic echocardiogram was performed, and it revealed a 17x22 mm mobile mass on the mitral valve, which was compatible with vegetation (Figure 1, 2). Transesophageal echocardiography (TEE) was performed to confirm the diagnosis of IE. Patent foramen ovale (PFO) was observed in the interatrial septum on TEE. Vegetation appearance and moderate mitral regurgitation were observed on the mitral valve. The patient was hospitalized with a preliminary diagnosis of IE. Laboratory results showed leukocytosis (white blood cells  $17 \times 10^9/L$ ), elevated C-reactive protein (56 mg/L), and increased erythrocyte sedimentation rate (95 mm/h). *Staphylococcus aureus* was detected in two separate blood cultures. The patient was diagnosed with definitive IE according to the modified Duke criteria (1), two major criteria were met with positive blood culture and vegetation. Mitral valve replacement was performed with



**Figure 1:** On the mitral valve, the mass is compatible with the vegetation (arrow).

RV: Right ventricle, RA: Right atrium, LA: Left atrium, LV: Left ventricle



**Figure 2:** The entrance of the mobile vegetation into the left ventricle is observed (arrow).

RV: Right ventricle, RA: Right atrium, LA: Left atrium, LV: Left ventricle

the agreement of the cardiac medical council. 1,000 mg IV vancomycin treatment was administered 3x1 (3,000 mg/day). The patient was discharged on the 27<sup>th</sup> day. Routine check-ups were recommended to the patient after discharge.

## DISCUSSION

The diagnosis of IE is made using modified Duke criteria (1). For the diagnosis of IE, the patient must fulfill either: 2 major, 1 major plus 3 minor, or 5 minor criteria. Two major criteria, one is positive blood culture consistent with IE, and the other is the demonstration of findings such as vegetation, intracardiac abscess, or valve regurgitation on echocardiography. Minor criteria are the presence of predisposing factors such as heart disease or IV drug use, body temperature  $>38$  °C, vascular events (intracranial hemorrhage, Janeway lesions), immunological events (Osler nodules, Roth spots, rheumatoid factor positivity), and microbiological evidence such as blood culture positivity that does not meet major criteria. Since there were 2 major criteria seen in this patient, the diagnosis was definitive IE (1, 4). According to most studies, *S. aureus* is the most common cause of IE, accounting for 26.6% of all cases (3). Viridans streptococci (18.7%), other streptococci (17.5%), and enterococci (17.5%) are the next most common causes of IE (10.5%) (3). These pathogens cause almost 90% of all cases of endocarditis (3). *S. aureus* is also the most prevalent pathogen, particularly in IV drug-associated IE cases (6). There are predisposing factors that contribute to the onset of IE, such as previous IE history, dental infection, cardiac pacemaker, prosthetic heart valve, or congenital structural heart disease (7). Moreover, IV-applied drugs, which cause bacterial contamination of the heart through the blood, also become the leading risk factor of IE (7). In this case, our patient does not have any structural predisposing factors in the mitral valve for the onset of IE. Therefore, IV drug usage appears to be the most important predisposing factor. IV drug-associated IE turns out to be a predisposing factor in 10% of all IE cases in developed countries (8). In cases of IE related to using IV drugs, the tricuspid valve is affected the most often; however, the mitral or aortic valves can also be affected, which in our patient, we determined mitral valve vegetation (9).

Interestingly, the tricuspid valve was free of vegetation. We explained this rare condition with the existence of a PFO that we observed in TEE; however, this situation can be explained by hematogenous spread, although it is rare. This case illustrates the need for considering left-sided valve endocarditis in IV drug abusers with septicemia, even if the tricuspid valve shows no evidence of vegetation (10).

The treatment of IE generally consists of antimicrobial therapy and is arranged for the pathogen obtained from

the blood culture (11). The duration of treatment may vary depending on the type of valve involved and the isolated pathogen; however, in IV drug-related IE, antibiotic treatment is usually 4-6 weeks long (12). As in our case, *S. aureus* is the most observed pathogen in blood cultures. According to the latest treatment protocols in Turkey, cefazolin is the first-line treatment for methicillin-sensitive *S. aureus* IE (13). Daptomycin should be preferred in patients with anaphylactic hypersensitivity reactions to  $\beta$ -lactams. In prosthetic valve IE, a combination of cefazolin, gentamicin, and rifampicin is suggested (13). A combination of vancomycin and cefazolin can be prescribed to patients with methicillin-resistant *S. aureus* IE, particularly in cases of persistent bacteremia (>3-7 days) (13).

Although patients with IE require surgical treatment, the timing of surgical intervention varies according to the surgical indication. In some cases, surgical intervention is performed urgently 24 hours after admission, while in some cases, elective surgery can be performed within 7-14 days (14). Depending on the affected region, the indications for surgical intervention and the type of surgery to be performed are different (13, 15). In this case, the mitral valve on the left side of the heart was affected. The most common indications for surgery in patients with IE are heart failure, prevention of embolism, and uncontrollable/invasive infections caused by resistant microorganisms (13, 16). Our patient underwent surgery due to the observation of significantly larger than 10 mm vegetation on the mitral valve with moderate mitral regurgitation.

Antimicrobial prophylaxis is recommended before hemorrhagic intraoral procedures in patients with predisposing cardiac conditions that may result in IE (previous IE history, presence of artificial heart valve, heart transplant recipients with valvulopathy, and cyanotic congenital heart diseases) (17). For prophylaxis, 30-60 minutes before the dental procedure, amoxicillin/ampicillin can be administered to patients who are not allergic to  $\beta$ -lactams intravenously or orally 2 gr in adults, 50 mg/kg in children (18). If the patient is allergic to  $\beta$ -lactams, clindamycin can be given 600 mg in adults and 20 mg/kg in children (18).

It is critical to determine the prognosis of a patient diagnosed with IE in terms of both treatment management and estimation of mortality risk. The patient should be evaluated at the time of diagnosis, in the first week following antibiotic therapy, and before discharge from the hospital. According to the simplified risk score used in the evaluation, plans such as aggressive treatment, early surgery, and transfer to the intensive care unit are considered (13). Poor prognosis markers can be classified under three headings as patient-related variables (aging, prosthetic heart valve, diabetes mellitus),

complications of IE (heart failure, renal failure, stroke, sepsis), and etiological pathogenic microorganisms (*S. aureus*, fungus) (19). The prognosis of artificial valve endocarditis is worse than natural valve endocarditis because it is more difficult to diagnose and treat (13). In addition, clinical studies show that left-sided IE has a worse prognosis than right-sided IE (15).

In the case we presented, surgery was decided because IE caused mitral valve regurgitation and had large, mobile vegetation. In conclusion, IE should be considered in the etiology of fever, unexplained worsening of general condition, and newly developed heart murmur in people using IV drugs.

**Ethics Committee Approval:** N/A

**Informed Consent:** Informed verbal consent was obtained from the next of kin.

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

**Author Contributions:** Concept: B.Ş., U.Y., S.A., Design: B.Ş., U.Y., S.A., Supervision: B.Ş., U.Y., S.A., Resources: B.Ş., U.Y., S.A., Materials: B.Ş., U.Y., S.A., Data Collection and/or Processing: B.Ş., U.Y., S.A., Analysis and/or Interpretation: B.Ş., U.Y., S.A., Literature Search: B.Ş., U.Y., S.A., Writing Manuscript: B.Ş., U.Y., S.A., Critical Review: B.Ş., U.Y., S.A.

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In the article by Özkan et al., entitled "An Investigation on the Anticancer Effect of Spider Web in Human Cervical Cell Line" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 50-3" is corrected as "Turkish Med Stud J 2019;6(1):1-11".

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In the article by Demirel et al., entitled "Systemic Cannabidiol Does Not Reduce Compound 48/80-Induced Itching Behavior in Mice" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 54-7" is corrected as "Turkish Med Stud J 2019;6(1):12-7".

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In the article by Avul et al., entitled "A Case Report: The Role of Prostate-Specific Membrane Antigen Labeled Theranostic Agents in the Diagnosis and Treatment of Prostate Cancer" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 69-75" is corrected as "Turkish Med Stud J 2019;6(1):31-6".

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DOI: 10.4274/tmsj.galenos.2019.06.01.06

In the article by Kılıççalan et al., entitled "Caenorhabditis Elegans and Angiogenesis" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 79-84" is corrected as "Turkish Med Stud J 2019;6(1):37-41".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e001**

DOI: 10.4274/tmsj.galenos.2019.06.01.01

In the article by Özkan et al., entitled "An Investigation on the Anticancer Effect of Spider Web in Human Cervical Cell Line" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 50-3" is corrected as "Turkish Med Stud J 2019;6(1):1-11".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e002**

DOI: 10.4274/tmsj.galenos.2019.06.01.02

In the article by Demirel et al., entitled "Systemic Cannabidiol Does Not Reduce Compound 48/80-Induced Itching Behavior in Mice" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 54-7" is corrected as "Turkish Med Stud J 2019;6(1):12-7".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e003**

DOI: 10.4274/tmsj.galenos.2019.06.01.03

In the article by Özyiğit et al., entitled "Evaluation of Malnutrition Statuses in Systolic Heart Failure Patients" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 58-63" is corrected as "Turkish Med Stud J 2019;6(1):18-24".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e004**

DOI: 10.4274/tmsj.galenos.2019.06.01.04

In the article by Kolotylo et al., entitled "The Influence of Intercurrent Diseases on the Course of HIV in Association with Active Tuberculosis" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 64-8" is corrected as "Turkish Med Stud J 2019;6(1):25-30".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e005**

DOI: 10.4274/tmsj.galenos.2019.06.01.05

In the article by Avul et al., entitled "A Case Report: The Role of Prostate-Specific Membrane Antigen Labeled Theranostic Agents in the Diagnosis and Treatment of Prostate Cancer" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 69-75" is corrected as "Turkish Med Stud J 2019;6(1):31-6".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e006**

DOI: 10.4274/tmsj.galenos.2019.06.01.06

In the article by Kılıççalan et al., entitled "Caenorhabditis Elegans and Angiogenesis" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 79-84" is corrected as "Turkish Med Stud J 2019;6(1):37-41".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e007**

DOI: 10.4274/tmsj.galenos.2019.06.01.07

In the article by Tsagkaris, entitled "Letter to the Editor" that was published in the February 2019 issue of Turkish Medical Student Journal, citation information was wrongly written due to a publishing software program error. The Editorial Board reviewed the case and "Turkish Med. Stud. J. 2018; 5: 69-75" is corrected as "Turkish Med Stud J 2019;6(1):42".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e008**

DOI: 10.4274/tmsj.galenos.2019.06.02.04

In the article by Mutlu et al., entitled "A Newborn with Esophageal Atresia, Tracheoesophageal Fistula and Feeding Problems" (Turkish Med Stud J 2019;6(2);60-3.) Figure 1 was reflected on the y axis by mistake and caused a misunderstanding like the patient had situs inversus. The figure is corrected as follows:

**DOI: 10.4274/tmsj.galenos.2022.09.01.e009**

In the article by Özkan et al., entitled "Evaluating Orthorexia Tendency Among Trakya University Medical School Students" that was published in the January 2015 issue of Turkish Medical Student Journal, the name of an author was wrongly written. The Editorial Board reviewed the case and "Atila Ülkücü" is corrected as "Attila Ülkücü".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e010**

DOI: 10.4274/tmsj.galenos.2020.07.01.06

In the article by Göztepe et al., entitled "Arrow Cause of Angina Pectoris: Single Coronary Artery in Elderly Patient" that was published in the February 2020 issue of Turkish Medical Student Journal, the name of the article was wrongly written. The Editorial Board reviewed the case and "Arrow Cause of Angina Pectoris: Single Coronary Artery in Elderly Patient" is corrected as "A Case Report: Single Coronary Artery in Elderly Patient".

**DOI: 10.4274/tmsj.galenos.2022.09.01.e011**

DOI: 10.4274/tmsj.galenos.2021.08.01.04

In the article by Tan et al., entitled "Fear of COVID-19 Among Medical Students and Associated Factors" that was published in the February 2021 issue of Turkish Medical Student Journal, protocol code was wrongly written. The Editorial Board reviewed the case and "Protocol Code: TÜTF-BAEK 2020/440" is corrected as "Protocol Code: TÜTF-BAEK 2020/448".

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NOTES

A series of horizontal dotted lines provided for taking notes.



