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Phone: +90 (284) 235 76 53
E-mail: tmsj@trakya.edu.tr

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CONTENTS

EDITORIAL

Dear readers,

I would like to present to you TMSJ's October issue of 2021. In this issue, you will find 11 articles: consisting of 1 editorial, 3 reviews, 4 original articles, and 3 case reports. Below you can find information about these articles.

Postpartum thyroiditis is the most common endocrine disorder associated with pregnancy. Therefore, Çelik et al. want to draw attention to postpartum thyroiditis, which is an important disease since it is the most common pregnancy-related endocrine disorder that occurs in women in the postpartum period, is seen in approximately 8% of pregnancies, and is usually not symptomatic in the first six weeks postpartum. Güvenç et al. aim to discuss to questions such as whether estrogen hormone therapy is effective on coronary artery calcification and whether there is a relationship between coronary artery calcification and osteoporosis in post-menopausal woman. Molecular mechanisms of the effects of estrogen on coronary artery calcification and osteoporosis should be understood thoroughly to answer these questions. Therefore, they focused on the molecular mechanisms of estrogen on coronary artery calcification and osteoporosis, and they explained the efficiency of estrogen hormone therapy on coronary artery calcification in post-menopausal women. Cengiz et al. want to show the effects of deficiencies of some vitamins and minerals, effects of vegetarian diet on the cardiovascular system, possible effects of vegetarian diet on cardiac diseases, as well as the effects of soy protein, which is consumed by vegetarians, on heart function are investigated.

İzzettinoğlu et al. aim to clinically and histopathologically examine eyelid lesions and evaluate the consistency of clinical examination by comparing the provisional diagnoses of patients with their postoperative histopathology results. Kılıççalan et al. aim to reveal the effects of acyclovir on angiogenesis and to assess the experimental doses. İzzettinoğlu et al. want to analyze the clinical characteris¬tics, examination findings, and outcomes of the patients diagnosed with phacomorphic glaucoma in the tertiary ophthalmology clinic of Trakya University Hospital. Bardakçı et al. share their findings on the evaluation of demographic, clinic and genetic characteristics of patients admitted to Trakya University Hospital with hypertrophic cardiomyopathy.

Of our 3 case reports, Kavakbasi et al. report the case of a 58-year-old female patient with treatment-refractory depression and post-traumatic stress disorder, who responded neither to unilateral electroconvulsive therapy nor to multiple antidepressant agents during several inpatient treatments. However, she achieved remission after bilateral electroconvulsive therapy. Özyiğit et al. present a case of a heart failure patient with a hydatid cyst of the lung, mimicking a phantom tumor. Peripartum cardiomyopathy is a rarely seen pregnancy-related myocardial disorder. The diagnosis is usually challenging and is made by exclusion. Yüksel et al. share a case of a patient with peripartum cardiomyopathy as a result of a successful treatment plan.

We are proud to present you the last issue of 2021. After this issue, my duty as Editor-in-chief in TMSJ comes to an end. I hand over my duty to Beliz Koçyiğit. I sincerely believe that they will do great things.

Hilal Sena Çifcibaşı
Editor-in-Chief, Turkish Medical Student Journal
Trakya University School of Medicine, Edirne, TURKEY

Address for Correspondence: Hilal Sena Çifcibaşı, Trakya University School of Medicine, Edirne, TURKEY
e-mail: hilalsena98@gmail.com
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ORCID iD of the author: HSÇ: 0000-0002-9507-1092.

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POSTPARTUM THYROIDITIS

Onur Çelik, İbrahim Kılıççalan

Gülhane School of Medicine, University of Health Sciences, Ankara, TURKEY

ABSTRACT

Postpartum thyroiditis is an autoimmune disease of the thyroid gland seen in approximately 8% of women in the postpartum period. Postpartum thyroiditis is a triphasic disease consisting of hyperthyroid, hypothyroid, and euthyroid phases. The pathogenesis of postpartum thyroiditis is not known exactly. However, there are various mechanisms related to pathogenesis. One of these is related to the fetal cell/DNA circulating in the maternal blood to settle in the thyroid gland and the maternal immune system to develop an autoimmune reaction against the thyroid gland in the postpartum period. During pregnancy, fetal cells settle in the thyroid gland and no reaction occurs due to pregnancy-related immunosuppression. Postpartum thyroiditis occurs because immunosuppression disappears in the postpartum period. The method of examining fetal cell/DNA in maternal blood during pregnancy is a non-invasive prenatal test. The non-invasive prenatal testing is a screening test used to detect chromosomal anomalies and some other chromosomal defects. However, there is to our knowledge, not enough studies in the literature directly investigating the relationship between the number of fetal cells/DNA in maternal blood and the development of postpartum thyroiditis. Having reviewed the literature around this topic it can be assumed that there can be a difference in the level of damage in the thyroid gland in the postpartum period, depending on the level of difference in the number of fetal cells in the thyroid gland. In addition, future studies will pave the way for studies on the relationship between autoimmune diseases occurring in the post-pregnancy period and the number of fetal DNA/cells in maternal blood during pregnancy. Therefore, an early diagnosis of pregnancy-related autoimmune diseases will be enabled. ***Keywords:*** Postpartum thyroiditis, pregnancy, hyperthyroidism, hypothyroidism, prenatal diagnosis

INTRODUCTION

Postpartum thyroiditis (PPT) is an autoimmune destructive subacute lymphocytic thyroiditis that develops in a euthyroid woman within 12 months of the postpartum period and has an overall prevalence of 8% (1-3). The prevalence of PPT differs between countries. For example, while its incidence is 1.1% in Thailand, it is 13.3% in Brazil (4). These differences are thought to be related to the postpartum follow-up period and conditions such as iodine intake (4). However, there are high-risk groups for PPT. These risk groups are; type I diabetes patients (prevalence 19.9%), patients with positive family history (20%), and/or previous history of PPT (42.4%) (5). PPT is the most common endocrine disorder associated with pregnancy (3). PPT is accelerated by the rebound effect in the postpartum period after pregnancy-related partial immunosuppression in individuals at risk for autoimmune thyroiditis (6). Signs of PPT are usually not evident in the first six weeks postpartum (3). Therefore, clinicians should be careful about PPT in this period.

Postpartum thyroiditis is triphasic due to changes in hormone levels. Hyperthyroidism is seen first and caused by an excessive and rapid release of thyroid hormone into the blood due to the destruction of thyroid cells. Later, hypothyroidism is observed, which shows that the thyroid gland cannot produce enough hormones due to cell destruction. At the end of 12-18 months after birth, the patient becomes euthyroid again (7). However, 25-30% of women who develop PPT have a risk of developing permanent hypothyroidism within 5-10 years (3, 8). Therefore, women with a history of PPT should be examined at regular intervals. This review was written to draw attention to PPT, which is an important disease since it is the most common pregnancy-related endocrine disorder that occurs in women in the postpartum period, is seen in approximately 8% of pregnancies, and is usually not symptomatic in the first six weeks postpartum.

PATHOGENESIS

Postpartum thyroiditis is a type of thyroiditis with histological features similar to Hashimoto's thyroiditis and lymphocytic infiltration (3). However, it differs from Hashimoto's thyroiditis in that, it does not have the same degree of fibrosis and follicular atrophy as Hashimoto's thyroiditis (9). When women who had PPT were examined, it was revealed that most of the women had autoimmune changes in the thyroid gland before pregnancy, and there was a relationship between PPT and anti-thyroid peroxidase antibodies (TPO-Ab) (3). However, it is not clear that TPO-Ab are the direct causes of PPT. Except for PPT, TPO-Ab are observed in all forms of autoimmune thyroid disease, including Hashimoto's thyroiditis and Graves' disease. The level of TPO-Ab correlates with the severity of lymphocytic infiltration in the thyroid gland and TPO-Ab can induce antibody-dependent cell-mediated cytotoxicity (3, 10).

Apart from TPO-Ab, various factors such as maternal immune modulators and environmental factors also play a role in the pathogenesis of PPT. It has been shown that the CD4/CD8 ratio and the number of activated T cells are higher in women with PPT than in healthy women (11). However, when TPO-Ab-positive women with PPT were compared with TPO-Ab-positive euthyroid women, it was shown that plasma cortisol levels at the 36th week of pregnancy was lower and gamma interferon levels were higher in

Address for Correspondence: İbrahim Kılıççalan, Gülhane School of Medicine, University of Health Sciences, Ankara, TURKEY
e-mail: ibrahimklccalan@gmail.com
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ORCID iDs of the authors: OÇ: 0000-0002-6100-8597; İK: 0000-0001-7086-4988.

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TPO-Ab-positive women with PPT (3). This situation reveals that the risk of developing PPT is higher in the group with less immunosuppression during pregnancy than TPO-Ab-positive women (11).

The appearance of fetal cells in the maternal circulation is called fetal microchimerism (12). Fetal cells begin to appear in the maternal circulation one week after the onset of pregnancy (12). Studies have shown the presence of fetal cells in the thyroid gland in women with autoimmune thyroid disorders (12, 13). Fetal cells, which pass into maternal blood during pregnancy, migrate to the thyroid gland and then settle in the thyroid gland. Intrathyroidal fetal cells survive due to immunosuppression during pregnancy. In the postpartum period, the immunosuppressed state disappears, and the maternal immune system is activated against fetal intrathyroidal cells (12). As a result, thyroid gland destruction and PPT occur. This theory is another theory about the development of PPT.

There are also various studies on the role of environmental factors such as smoking in the pathogenesis of PPT. A positive relationship was found in the meta-analysis by Vestergaard (14).

SIGNS AND SYMPTOMS

Postpartum thyroiditis is a triphasic disease, including hyperthyroidism, hypothyroidism, and euthyroidism. Therefore, the symptoms in patients differ according to the period of the disease. Findings in PPT usually do not appear in the first six weeks (3). Later, due to the destruction of the thyroid gland, symptoms appear in the first 1-4 months of the postpartum period. Hyperthyroidism symptoms occur in the first month of the postpartum period and last about 1-2 months (15, 16). During this period, patients may experience irritability, palpitations, anxiety, unexplained weight loss, tremor, insomnia, and heat intolerance (16). However, the findings of hyperthyroidism in PPT are usually mild (3). For this reason, it may not be noticed or may be misinterpreted by the patients depending on post-pregnancy changes. After the postpartum period of thyrotoxicosis, hypothyroidism occurs. The hypothyroid period occurs between the third and the ninth months of the postpartum period and lasts for four to six months (3, 16). During this period, the patient may experience low energy, forgetfulness, lack of concentration, cold intolerance, memory problems, constipation, weight gain, and dry skin, or the patient may be asymptomatic (16). The relationship between PPT and depression has not been demonstrated (17). However, since the findings are more pronounced in the hypothyroid period, most PPT patients consult a clinician during the hypothyroid phase. Most patients become euthyroid approximately 12 months after giving birth (16).

DIAGNOSIS

Laboratory Tests

Since PPT is a triphasic disease, the findings in laboratory tests change according to the stages of the disease. In the thyrotoxicosis phase, which is the first phase of the disease, thyroid-stimulating hormone (TSH) is suppressed, and thyroxine (T4) levels are high. In the hypothyroid phase, T4 and triiodothyronine (T3) levels are observed to be low. In the third phase, the euthyroid phase, T3 and T4 levels are within the normal range. In addition, most patients are TPO-Ab-positive (17, 18). However, thyroglobulin antibody can also be observed as positive (17).

Imaging Findings

Radioactive iodine uptake is low in the thyrotoxic phase of PPT (18). When the thyrotoxic phase is over, radioactive iodine uptake in the hypothyroid phase is found to be normal or high (18). On the ultrasonography (USG) of PPT, heterogeneous hypoechogenic thyroid tissue is often observed (19). In the study of Shahbazian et al. (19), thyroid volume was found to be 77% higher in the initial period of PPT compared to the control group. However, after remission of the disease, the mean thyroid volume was found to be reduced by 25% (19). USG is recommended as an adjunct to laboratory tests in PPT (18, 19).

Non-Invasive Prenatal Test (NIPT)

In most countries, USG and maternal serum screening markers are used in the first and/or second trimester to detect chromosomal anomalies and other congenital anomalies. There is a 2-7% false-positive risk in these screening tests (20). Invasive diagnostic tools such as chorionic villus sampling (CVS) and amniocentesis are used when positivity is detected in these screening tests. CVS is typically done between the 11th to 14th weeks, while amniocentesis is performed after the 15th week of gestation (20). The risk of miscarriage due to these tests is approximately 1-2 ‰ depending on the procedure (21, 22). This situation reveals the importance of developing new tests for diagnosis and screening. One of the tests developed for this purpose is the non-invasive prenatal test (NIPT). NIPT relies on the presence of circulating free DNA (cfDNA) in maternal blood. The presence of fetal cfDNA in maternal blood was first shown in 1997 (23). NIPT is a screening test used to examine the fetal cfDNA in the maternal blood and to detect fetal chromosomal aneuploidies such as trisomy 13 (Patau syndrome), trisomy 18 (Edwards' syndrome), trisomy 21 (Down syndrome) (23). The false-positive rate of NIPT (1-3%) is lower than pregnancy screening tests and there is no risk of miscarriage (20). NIPT was developed to avoid direct contact with the fetus/placenta and not to compromise the health of the fetus (24). NIPT is based on examining fetal DNA in a blood sample taken from the mother during pregnancy (24). Fetal DNA can be analyzed from the 9th week of gestation (25). Fetal DNA samples can be obtained from maternal plasma and serum samples greater than 10 μL (23, 24).

The fetal fraction in maternal blood is important in NIPT. Fetal fraction is the ratio of fetal cfDNA to total cfDNA in maternal blood. Fetal cfDNA originates from placental trophoblasts. Therefore, NIPT can be considered as a test that examines fetal DNA samples that have passed into maternal blood (24, 26). Fetal fraction should be at least 4% in NIPT tests to be considered successful (23, 25, 27). However, studies that investigated the first 10-14 days of pregnancy found that fetal fraction increased by more than 10% in first weeks of gestation (fetal fraction may be affected depending on factors such as the weight of the mother, singleton, or multiple pregnancies.) (23). NIPT is a very important test in early diagnosis and its sensitivity and specificity is greater than 99% in the detection of common chromosomal anomalies such as trisomy 13, trisomy 18, trisomy 21 (28).

TREATMENT

Treatment of PPT requires extra attention as women breastfeed their infants. If symptoms are mild during the first phase of PPT, hyperthyroidism (thyrotoxicosis), treatment is usually not needed. However, if symptoms are severe, beta-blockers can be used to control symptoms (18). After the patient has entered the hypothyroid phase, if necessary, L-Thyroxine (L-T4) can be used for symptomatic treatment. If L-T4 is not started, TSH levels should be checked every 1-2 months until the 12th postpartum month (29). The use of L-T4 up to 12 months postpartum is still under discussion (18). The

use of L-T4 in patients should be evaluated according to the risk of developing permanent hypothyroidism (29). When the patient enters the euthyroid phase, the patient should be followed up. In case of permanent hypothyroidism, patients should use L-T4 regularly and TSH levels should be monitored at regular periods (29).

CONCLUSION

Postpartum thyroiditis is an autoimmune, triphasic (hyperthyroid phase, hypothyroid phase, and euthyroid phase) disease observed in 8% of pregnant women (1-3). Various factors are involved in the pathogenesis of PPT. These factors are; TPO-Ab, fetal microchimerism, and smoking. However, there are no studies on the number of fetal cfDNA in maternal blood and the risk of developing PPT. Having reviewed the literature around this topic it can be assumed that there can be a difference in the level of damage in the thyroid gland in the postpartum period, depending on the number of fetal cells in the thyroid gland. In addition, future studies will pave the way for studies on the relationship between the emergence of autoimmune diseases in the post-pregnancy period and fetal cfDNA level in maternal blood during pregnancy. Therefore, an early diagnosis of pregnancy-related autoimmune diseases will be enabled.

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EFFECTS OF ESTROGEN ON CORONARY ARTERY CALCIFICATION AND THE RELATIONSHIP BETWEEN OSTEOPOROSIS AND CARDIOVASCULAR DISEASES IN POSTMENOPAUSAL WOMEN

Alican Güvenç[1], Ceren Yılmaz[1], Buse Balta[1], Zeynep Yıldız[1], Selma Arzu Vardar[2]

[1]Trakya University School of Medicine, Edirne, TURKEY
[2]Department of Physiology, Trakya University School of Medicine, Edirne, TURKEY

ABSTRACT

Estrogen deficiency is known to be one of the causes of cardiovascular disease and osteoporosis in postmenopausal women. Coronary artery calcification is one of the major factors of cardiovascular disease. The studies related to the effects of estrogen on coronary artery calcification and the possible relation between osteoporosis and cardiovascular disease rapidly increased in recent years. Estrogen levels decrease in postmenopausal women and can lead to an increased risk of cardiovascular disease. Estrogen could affect cardiovascular diseases by mediating the receptor activator of nuclear factor-kappa B ligand-osteoprotegerin system in vascular smooth muscle cells and autophagy in cardiomyocytes. Current evidence indicates that estrogen has an increasing effect on bone mineral density by multiple biochemical pathways: increasing calcium absorption in the gastrointestinal system, decreasing excretion of calcium in the kidneys, reducing bone resorption, such as enchanting osteoblasts, suppressing osteoclasts by inhibiting proinflammatory cytokines, and inhibiting the activity of osteoclasts by essentially inhibiting the receptor activator of nuclear factor-kappa B ligand-osteoprotegerin system. Recent studies showed a significant relationship between coronary artery calcification and osteoporosis due to estrogen's role in these pathogeneses, which can be prevented by using estrogen hormone therapy for post-menopausal women. In this review, we focused on the molecular mechanisms of estrogen in the development of coronary artery calcification and osteoporosis and the effects of estrogen hormone therapy on cardiovascular diseases in postmenopausal women. ***Keywords:*** Menopause, osteoporosis, vascular calcification, estrogen replacement therapy, cardiovascular diseases

INTRODUCTION

Cardiovascular diseases and osteoporosis caused by estrogen deficiency are seen widely in postmenopausal women, causing numerous health risks (1-6). Cardiovascular diseases are correlated with fat deposits and plaques formed in the arteries, which can lead to an increased risk of myocardial infarction (2, 3). Moreover, coronary artery calcification (CAC) is one of the major causes of cardiovascular diseases since it forms calcium plaques in coronary arteries and causes atherosclerosis (4).

Calcium plaque in the arteries contains fat, cholesterol, calcium, and other elements found in the blood (5). In time, plaque solidifies, enlarges, thus decreasing the lumen of the arteries, causing impaired blood flow (5). This situation may end up with ischemia or myocardial infarction (5). According to the World Health Organization's (WHO) data, cardiovascular disease is the most common cause of death in the world, causing over 18 million deaths per year which corresponds to 31 percent of total deaths worldwide (5).

Additionally, estrogen deficiency in postmenopausal women can commonly lead to osteoporosis (6, 7). It has been described by WHO that patients who have a bone mineral density (BMD) below -2.5 standard deviation, calculated by dual-emission X-ray absorptiometry, is classed as having osteoporosis (6). Thus, an increased risk of bone fractures and destruction of the microstructure of bones are observed in osteoporosis (6, 7). However, the relationship between postmenopausal osteoporosis and CAC in postmenopausal women is unclear (6, 8).

Here, we want to draw attention to questions such as whether estrogen hormone therapy is effective on CAC and whether there is a relationship between CAC and osteoporosis in post-menopausal woman. Molecular mechanisms of the effects of estrogen on CAC and osteoporosis should be understood thoroughly to answer these questions. Therefore, we focused on the molecular mechanisms of estrogen on CAC and osteoporosis, and we explained the efficiency of estrogen hormone therapy on CAC in post-menopausal women.

THE EFFECT OF ESTROGEN ON CORONARY ARTERY CALCIFICATION

It is known that CAC is an indicator of coronary plaque burden (9). CAC has been observed more frequently in men than women and its prevalence increases among older-aged men (10). There are many studies about how estrogen affects coronary artery calcification. One of the studies related to osteoprotegerin (OPG) and receptor activator of nuclear factor-kappa B ligand (RANKL) reported that OPG and RANKL are new associates of the tumor necrosis factor signaling superfamily and both are thought to take part in vascular calcification and bone remodeling (11).

Address for Correspondence: Alican Güvenç, Trakya University School of Medicine, Edirne, TURKEY
e-mail: alejhonreliance@gmail.com
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ORCID iDs of the authors: AG: 0000-0003-4450-5476; CY: 0000-0002-7371-769X; BB: 0000-0002-2386-1861; ZY: 0000-0003-4488-7451; SAV: 0000-0002-1073-1718

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Although Bakhireva et al. (11) demonstrated that RANKL and OPG's effects on BMD-CAC are minimal, previous studies have shown the importance of RANKL and OPG. As shown in Figure 1, matrix Gla protein (MGP) is a protein that decreases vascular calcification, and bone morphogenetic protein-2 (BMP-2) is a protein that increases vascular calcification. It is shown by Osako et al. (12) that RANKL decreases MGP and increases BMP-2; therefore, RANKL increases vascular calcification non-directly. Osako et al. (12) have also reported that the ratio of RANKL mRNA and BMP-2 in mice that have gone through ovariectomy, and therefore have an estrogen deficiency, have been observed significantly higher compared to controls. Additionally, CAC and atherosclerosis have been observed in mice that have been ovariectomized (12). Hence, estrogen has been demonstrated to have a counter effect on CAC by mediating the RANKL-OPG system (12).

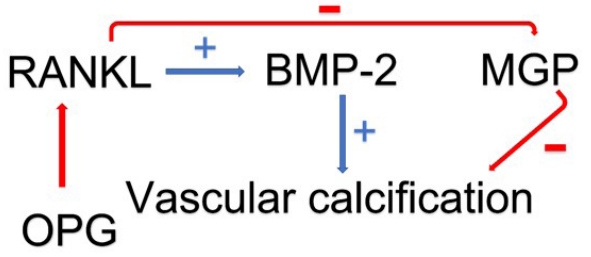

Figure 1: Molecular mechanisms of the RANKL-OPG system. ***OPG:*** Osteoprotegerin, ***RANKL:*** Receptor activator of nuclear factor-kappa B ligand, ***BMP-2:*** Bone morphogenetic protein-2, ***MGP:*** Matrix Gla protein

On the other hand, the main focus of current research is on the effect of heart fat on CAC. Heart fat is one of the causes of coronary artery disease, and the contents of heart fat increase after menopause (13). According to this research, using transdermal β17-estradiol positively affects the connection between pericardial adipose tissue accumulation and CAC progression (13). In addition, it has been observed that using oral conjugated equine estrogens might decelerate epicardial adipose tissue accumulation (13).

Another molecular research area on the possible effects of estrogen on calcification includes autophagy. Autophagy is defined as the self-destruction of a cell to obtain new and healthier cells. Autophagy functionally supports the inhibitory effects of estrogen on vascular calcification as demonstrated by Peng et al. (14). In addition, recent findings show that some molecular and functional alterations in the homeostasis-related proteins in cardiomyocytes are caused by a lack of estrogen (15). Deterioration of the calcium homeostasis cycle has been reported to have negative effects on cardiac function, therefore deterioration of the calcium homeostasis cycle causes pathological mechanisms of a variety of cardiovascular diseases (15).

ESTROGEN HORMONE THERAPY AND CORONARY ARTERY CALCIFICATION

Estrogen increases nitric oxide production, which vasodilates arteries and enhances vascular function, and lessens the development of atheroma by reducing endothelin-1 release and angiotensin-1-converting-enzyme activity, modulating ion channels, and reducing the modification of vascular remodeling processes (16). CAC is known as an important determinant of cardiovascular risk and it is known to be associated with atherosclerosis and future cardiac problems (17). Schierbeck et al. (18) found in their analyses of 1006 women in Denmark that hormone replacement therapy (HRT) users have decreased risk of mortality, heart failure, or myocardial infarction and no increase in venous thromboembolism, stroke, or cancer. Many studies have been conducted to study the association between estrogen and CAC in postmenopausal women (17, 19, 20). A previous study of 1064 patients aged 50-59 years showed that 537 of them received 0.625 mg/day estrogen and 527 of them received a placebo for 7.4 years (19). The results of this study have shown that women who took long-term estrogen therapy had a noticeably lower coronary artery calcification ratio (19). Similar to these findings, a study on 2213 postmenopausal women of Akhrass et al. (20) indicated that HRT users are very likely to have less coronary artery calcium scores and it has been observed that they unlikely have high coronary artery calcium scores. In another study on the younger aged midlife women compared to postmenopausal women showed a significant relationship between HRT usage and a decrease in coronary artery calcification (21). According to the findings above, estrogen HRT can be accepted as protective on coronary artery calcification among different age groups.

In a clinical study run by the Women's Health Initiative (WHI), no reduction was found in coronary heart disease between patients on HRT, but more effective distribution of low-density lipoprotein subclasses have been shown in blood lipid concentrations (22). To understand this finding better, the Healthy Women Study was carried out to study the prevalence of CAC and lipoprotein levels of women on HRT (22). Compared with nonusers, HRT users had higher levels of very-low-density lipoprotein particles (triglycerides) and did not have a better low-density lipoprotein subclass distribution, which may explain the failure of hormone therapy to be associated with a difference in CAC in our study or with a reduction in coronary heart disease risk in randomized clinical trials (22). The WHI study was a randomized clinical trial conducted among postmenopausal women aged 50-79 years (23). One group was given a placebo and the other group was given conjugated equine estrogen, and no significant association between estrogen therapy use and reduced risk of coronary heart disease was found (23). However, as an ancillary study, the WHI Coronary Artery Calcification Study found an association between estrogen use and reduced risk of coronary heart disease (23).

The effects of estrogen as a single hormone therapy agent or combination of other hormone agents have been investigated. In a study run by the WHI, it was found that the use of estrogen and progestin (combined) hormone therapy caused a minor but significant uprise in cardiovascular event risk, and in breast cancer risk in asymptomatic participants (24). Budoff et al. (24) carried out a study to investigate whether estrogen-alone hormone therapy affected cardiovascular risk. To do so, they separated participants into three groups; no hormone, estrogen, and progestin (combined), and estrogen-only hormone replacement therapy users (24). In this observational study, they also found that there was no benefit of combined therapy to reduce coronary heart risk compared to non-users (24). Interestingly, the level of atherosclerosis was found to be lower in participants using estrogen-only hormone replacement therapy than in those using combined therapy and not using replacement therapy (24).

In a previous study, the relationship between BMD and CAC in females who use or do not use estrogen hormone therapy has been compared with males (25). An inverse association of BMD and CAC was found only in participants who were using estrogen hormone therapy, whereas no statistically significant association was observed in both the female participants who were not taking hormone therapy and in male participants (25). According to the study, estrogen was found to increase BMD and reduce CAC (25).

The degree of the relationship between estrogen hormone therapy and BMD and CAC is not exactly known (25).

A study that investigates the link between HRT, CAC, and carotid intima-media thickness in postmenopausal women showed a low but not significant prevalence of CAC among estrogen hormone therapy users (26).

THE EFFECTS OF ESTROGEN ON OSTEOPOROSIS

Estrogen is effective in multiple mechanisms underlying the regulation of calcium homeostasis and bone remodeling to prevent osteoporosis. These critical biological mechanisms occur by enhancing calcium absorption in the gastrointestinal system and reducing the excretion of calcium from the kidneys (27, 28). Moreover, estrogen may negatively regulate the activity of osteoclasts (large bone tissue cells that are responsible for bone resorption) by the inhibition of some proinflammatory cytokines such as interleukin-1, interleukin-6, tumor necrosis factor-α, macrophage colony-stimulating factor, and PGE26. Thus, it is reported that bone resorption decreases with estrogen (29).

Additionally, according to current findings, the effects of estrogen on BMD may result from the regulator role of estrogen on OPG and its ligand RANKL which are shown as the new-found associates of the tumor necrosis factor-signaling family as mentioned above (30). Estrogen reduces bone resorption by inhibiting pro-resorptive cytokines and suppressing RANKL (30). In addition, it has been shown that estrogen boosts osteoclast apoptosis (31). Furthermore, estrogen positively regulates cell differentiation into the osteoblasts and mediates adipocyte lineage cells to shift into the osteoblast (32).

Likewise, one of the effects of estrogen on vascular tissues is the inhibition of vascular smooth muscle cells (VSMC) (29, 33). These cells are the progenitors of the osteoblast-like cells, and they generate matrix proteins such as osteocalcin, osteonectin, osteopontin that are responsible for vascular calcification (29, 33). Interestingly, suppression of tumor necrosis factor-α in bone tissues reduces the bone resorption, preventing osteoporosis; whereas in vascular tissues, the proliferation of VSMC decreases vascular calcification and reduces coronary heart disease risk by reducing the calcium burden (29, 33). In recent studies, scientists have found this reducing effect on vascular calcification with suppression of the VSMC proliferation only occurs in female animals (29, 33). According to previous findings, a relationship between vascular calcification and osteoporosis could be possible.

OSTEOPOROSIS AND VASCULAR CALCIFICATION

Recent studies suggest that mechanisms of osteoporosis may be related to vascular calcification in postmenopausal women (12, 34). Since CAC shares a similar cardiovascular disease risk with other vascular calcification types, such as general aortic calcification, the relationship between CAC and osteoporosis needs to be clarified.

As shown in Figure 2, menopause induces estrogen deficiency, causing an increase in RANKL levels in the vascular calcification signaling pathway. In this pathway, RANKL may trigger BMP-2 levels to increase and MGP levels to decrease during vascular calcification (12). Similarly, estrogen deficiency causes osteoporosis in postmenopausal by upregulating the RANKL signaling pathway (30, 35, 36).

Many studies in the latest literature reported an inverse relationship between BMD and aortic calcification (increased calcium burden in arteries) (37, 38). A study by Tankó et al. (38) reported that osteoporosis, which causes a high bone fracture risk in hips, may be a predictor of an increased risk factor for coronary heart diseases caused by aortic calcification. Furthermore, Schulz et al. (39) demonstrated that heart disease has been linked to osteoporosis and aortic calcification and that osteoporosis can be accepted as a significant predictor of a decrease in BMD.

Manson et al. (40) reported a statistically significant decrease in coronary heart disease risk in postmenopausal women who took equine estrogen compared to postmenopausal women who took a placebo. These results point to the mediator role of estrogen in CAC. Bakhireva et al. (25) reported a significant association between CAC and osteoporosis in postmenopausal women who use estrogen HRT. The study did not demonstrate a statistically significant association in men and postmenopausal women who has symptomless cardiovascular diseases and who do not use HRT (25). Furthermore, reports of Choi et al. (41) showed a statistically significant association between high-ranking coronary plaque burdens and low-ranking BMD in postmenopausal women, which was independent of the presence of cardiovascular disease and the age of the participants. Similarly, a previous study indicated that estrogen hormone therapy increased BMD and decreased hip and medical vertebral fractures, which gave notable information about the role of estrogen on osteoporosis (42).

Even though there are contradictory findings that have not found a statistically significant relationship between CAC and osteoporosis, further studies that include patients who have coronary heart disease or osteoporosis are needed (43, 44). These studies would be important in understanding the link between CAC and osteoporosis.

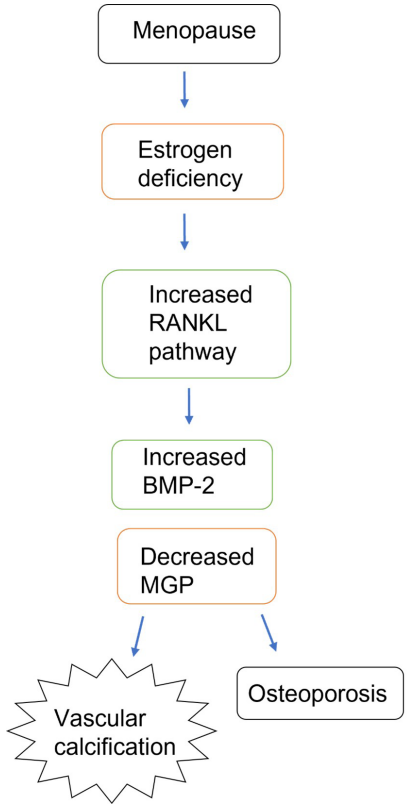

Figure 2: The relationship between vascular calcification and osteoporosis.
RANKL: Receptor activator of nuclear factor-kappa B ligand, ***BMP-2:*** Bone morphogenetic protein-2, ***MGP:*** Matrix Gla protein

CONCLUSION

In conclusion, decreasing estrogen levels in postmenopausal women may be responsible for creating an increased risk of cardiovascular disease. Estrogen could increase the risk of cardiovascular disease by upregulating the RANKL-OPG system in vascular smooth muscle cells and autophagy in cardiomyocytes. Additionally, regulation of calcium homeostasis is important since estrogen deficiency causes molecular and functional changes in calcium homeostasis-related proteins in cardiomyocytes. Estrogen therapy has been demonstrated to be effective on osteoporosis by similar biochemical pathways. Clarifying the association between osteoporosis and cardiovascular diseases in postmenopausal women is essential to better understand the efficiency of estrogen hormone therapy. Further studies are needed to achieve this.

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THE EFFECTS OF VEGETARIAN DIET ON THE CARDIOVASCULAR SYSTEM

Nazlıcan Cengiz[1], Tülay Ece Özçelik[1], Beyza Yılmaz[1], Nisanur Bayar[2], Selma Arzu Vardar[3]

[1]Trakya University School of Medicine, Edirne, TURKEY
[2]Trakya University School of Physiotherapy and Rehabilitation, Edirne, TURKEY
[3]Department of Physiology, Trakya University School of Medicine, Edirne, TURKEY

ABSTRACT

Vegetarianism is the refusal to eat meat and its products for various reasons. Furthermore, veganism is against eating and using all products derived from animals. Numerous studies have stated that plant-based nutrition reduces the risk of cardiovascular system diseases, but also cannot supply the requirement of some vitamins and minerals. Although a vegetarian diet may decrease the risk of cardiovascular diseases, the findings of the studies related to the low intake of protein, vitamins, or minerals should be taken into account in terms of harmful effects. In this review, the studies have been reviewed about the effects of plant-based nutrition on the human cardiovascular system. ***Keywords:*** Cardiovascular system, vegans, vegetarians, diet, plant proteins

INTRODUCTION

Vegetarianism is the refusal to eat meat (red meat, poultry, seafood, and the flesh of any other animal) (1). Vegetarians may be further sub-classified as vegans, pesco-vegetarians, lacto-vegetarians, lacto-ovo-vegetarians, and semi-vegetarians (2). Vegans avoid using or eating any animal products (2). Pesco-vegetarians consume fish and other seafood (2). Lacto-vegetarians eat dairy products; lacto-ovo-vegetarians eat dairy products and eggs (2). As another subgroup, semi-vegetarians usually follow a vegetarian diet but occasionally consume meat (2).

Some people think that consuming meat is unhealthy and that a vegetarian diet generally prevents diseases (3). Other common reasons for choosing vegetarian diets are animal welfare or rights, satisfying religious or spiritual needs, and saving the environment (3). The prevalence of vegetarianism varies around the world; roughly 5% of Americans, 8% of Canadians, 4.3% of Germans, and 30% of Indians follow a vegetarian diet (4-8). Vegan diet prevalence has been reported as 2% in the United States and less than 1% in Germany (4, 9).

Plant-based diets have documented health advantages (10). It decreases the serum cholesterol levels, blood pressure, and vegetarians have decreased cardiometabolic risk than omnivores (10). Vegetable and fruit intake frequency is inversely proportional to cardiovascular disease mortality, ischemic heart disease (IHD) mortality, stroke incidence, and stroke mortality (11). According to the studies, vegetarian diets decrease blood pressure compared to omnivorous diets (12). Lower blood pressure leads to a decrease in deaths from all causes, deaths from coronary heart disease (CHD), and stroke (12, 13).

In this review, the effects of deficiencies of some vitamins and minerals, effects of vegetarian diet on the cardiovascular system, possible effects of vegetarian diet on cardiac diseases, as well as the effects of soy protein, which is consumed by vegetarians, on heart function are investigated.

NUTRIENT PROFILES AND NUTRITIONAL DEFICIENCY OF VEGETARIANS

It is considered that vegetarian diets improve health and decrease the risk of cardiovascular diseases (CVDs) (14). On the other hand, a vegetarian diet may cause vitamin deficiency because vegetarians have lower intakes of protein, saturated fat, cholesterol, vitamin B12, vitamin D, zinc, calcium, and selenium (14).

Although veganism and vegetarianism exist all over the world, only in the past 50 years it was noticed that vegan and/or vegetarian diets lead to vitamin B12 deficiency (15). Vegans and vegetarians tend to have a vitamin B12 deficiency because their diets have a very low B12 content (15). Vitamin B12 can only be synthesized in nature by some bacteria found in the bowels of humans, therefore humans must provide the intake of vitamin B12 from their diet (15). Non-vegetarians receive vitamin B12 from meat, eggs, milk, and dairy products (15). Plant fertilization with manure might cause contamination with vitamin B12 synthesizing bacteria. Thus, organic vegetables can be a better source of vitamin B12 (15).

In a large-scale study, participants were stratified into non-vegetarian, semi-vegetarian, pesco-vegetarian, and strict vegetarian (16). Data on dietary patterns were collected, and nutrient profiles were presented. Results showed that pesco-vegetarians and non-vegetarians had the highest intakes of vitamin B12 and vitamin D while strict vegetarians had the lowest (16). Furthermore, intakes of calcium and iron were lowest in strict vegetarians (16). Conversely, strict vegetarians had the highest intakes of folate, soy protein, fiber, vitamin C, and vitamin E (16).

Address for Correspondence: Nazlıcan Cengiz, Trakya University School of Medicine, Edirne, TURKEY
e-mail: nazlicng.12@gmail.com
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ORCID iDs of the authors: NC: 0000-0003-0555-4603; TEÖ: 0000-0002-2048-2479; BY: 0000-0003-1886-5734; NB: 0000-0003-1986-9542; SAV: 0000-0002-1073-1718.

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Homocysteine is an amino acid that is produced through the demethylation of methionine and animal proteins contain plenty of methionine (17). It has been revealed that plasma homocysteine concentration is one of the independent risk factors of CHD (18). Vitamin B12 and some other B vitamins are necessary for homocysteine metabolism (19). Cobalamin (B12) as cofactor and folate (B9) as co-substrate are responsible for the remethylation of homocysteine (19). The other route for homocysteine metabolism is transsulfuration and it is a process that is dependent on vitamin B6 (20). Deficiency in these vitamins may result in the increment of plasma homocysteine concentration (21). Riboflavin (B2) has a role in the metabolism of other B vitamins and because of its role, riboflavin deficiency may affect homocysteine levels (22).

In a previous study, subjects were separated into groups such as vegetarians and non-vegetarians (21). Daily nutrient intakes' data was recorded and plasma homocysteine, vitamin B12, and folate levels were measured by obtaining fasting venous blood samples (21). The results of this study showed that vegetarian subjects had significantly higher mean plasma homocysteine concentration but lower vitamin B12 intakes than non-vegetarians (21). In addition, a positive correlation has been shown between animal protein intake and plasma homocysteine level in the non-vegetarian group (21).

VEGETARIANISM AND CARDIOVASCULAR DISEASES

Cardiovascular diseases refer to diseases of the heart and blood vessels (23). High intake of fat, saturated fats, and carbohydrates are important risk factors that increase the prevalence of CVDs (24). CVD is a medical term that includes diseases such as coronary heart disease (CHD), peripheral artery disease, cerebrovascular disease, rheumatic and congenital heart diseases, and venous thromboembolism CVDs are the major factor of global deaths (25, 26). It is responsible for one in four deaths across the world (26). The high prevalence of heart diseases was associated with lifestyle factors such as smoking, consuming refined foods, high animal fat content in the diet, and physical inactivity (27). According to a study, vegetarians have a 32% lower risk of getting CHD collated to non-vegetarians (28).

Diets containing high amounts of refined carbohydrates increase triglyceride concentration, while diets with a high fiber ratio decrease it (29). Dietary cholesterol is strongly associated with CVDs (29). The vegan diet has a cholesterol-lowering effect due to its low saturated fat content, soluble fiber, and other plant components (29). However, according to the findings of a previous study, although the total and low-density lipoprotein (LDL) cholesterol of vegans were at normal levels, high-density lipoprotein cholesterol level was low, homocysteine was high, and lipoprotein (a) level was negative in terms of coronary artery disease (CAD) (30). On the other hand, there are different opinions in studies about the effects of hyperhomocysteinemia (28-30). To understand the connection between hyperhomocysteinema and the vegan diet, the number of studies on this subject should be increased.

Atrial fibrillation has the highest prevalence in arrhythmias, and its risk factors include hypertension, CAD, and obesity (31). Plant-based nutrition reduces the likelihood of these risk factors. Improved vasodilatation, increased potassium intake, decreased blood viscosity are the main effects of plant-based diets for preventing hypertension (31). CAD is described as the blockage of the vessels that carry oxygen and nutrients to the heart (32). High-sensitivity C-reactive protein (hsCRP) is used as a marker of CAD (33). A high hsCRP level is an indicator of CAD risk (33). A study conducted with CAD patients with high hsCRP values showed that in addition to medical treatment, a vegan diet had lowered hsCRP levels (33). A vegan diet supports weight loss, glycemic control, and normalizing lipid values (33). However, studies examining medical treatment and diet together on CAD are limited (33). On the other hand, B12 deficiency is common among vegans and vegetarians (34). B12 deficiency may cause impaired carotid intima-media thickness and brachial flow-mediated endothelium-dependent dilation values compared to a similar group (34).

Vegetarian diets may not seem to be preventative for diseases, although it supports the treatment of type 2 diabetes (35). It is known that vegetarian diets combined with exercise can reduce the use of glucose in the body. Thus, plasma glucose levels and the use of glucoregulatory drugs decrease (34-36). A vegetarian diet also has beneficial effects without exercise. It reduces body weight and lowers blood lipids. Vegetarian diets are found more effective in glycemic control and treatment of type 2 diabetes compared to traditional diets (37, 38).

Trimethylamine N-oxide (TMAO) has been recently thought to be a prognostic marker for developing CVDs and most of the studies focus on this metabolite (39). TMAO is the form of trimethylamine (TMA) transformed by flavin monooxygenase in the liver (39). TMA is produced from substances such as choline, L-carnitine, betaine, and trimethyl lysine in the intestine (39). TMAO is a chemical compound that can accumulate in organs such as the heart and kidney (40). TMAO and its precursors are animal food items that originate mostly from fish, meat, egg, poultry, and milk (40). The amount of TMAO component is less in vegetarians because their diet contains fewer animal foods and these precursors (41). Preclinical studies showed that TMAO directly causes damage to the heart muscle and mitochondria (40). TMAO increases the risk of thrombosis and ischemic heart failure (HF) (40). In addition, studies indicate that a vegetarian diet avoids and cures HF (42).

In a meta-analysis by Miller et al. (43), it was observed that intake of egg yolks with diet increased urine and plasma TMAO concentrations. This study showed phosphatidylcholine, which is a type of choline in eggs, transforms TMA contrary to what is believed (43). These concentrations reach the highest level with consumption of 4-6 eggs (43). But they could not demonstrate a connection with increased TMAO levels and CVDs (43).

All dairy products, eggs, red meat, and processed meat include saturated fatty acids (44). In a randomized controlled study, it was revealed that plasma LDL cholesterol levels were raised by saturated fatty acids intake (44). Recent studies showed that a low-calorie vegetarian diet decreases LDL cholesterol levels and is efficient in preventing and treating cardiovascular system diseases (45). Conversely, cheese, eggs, and yogurt were linked to significantly lower IHD risk. Poultry, milk, and fish were not related to IHD (46). In a study carried out by Key et al. (46), it has been observed that when red meat and processed meat were consumed together, heart rate and IHD risk increased (46). Consumption of eggs reduces IHD risk in men but does not affect women (46). Yogurt and cheese were invertedly linked to IHD risk, but this relation was not significant in the study (46). Fatty acids and calcium in cheese generate insoluble soaps. It is thought that when saturated fatty acid absorption decreases, calcium binds to bile acids and diminishes enterohepatic circulation and cholesterol levels (44).

Vegetarianism is also preferred in different age groups and periods. It should be taken into consideration that nutritional needs vary depending on different periods of life and physical activity. If vegetarian people do not follow a proper diet it may have unfavorable health effects. In the studies with vegan and non-vegan athletes, there is no difference found in their performances (47). It has been observed that vegan athletes do not show any deficiency

compared to non-vegan athletes when they follow a suitable diet (47). A vegan athlete's relative wall thickness, as well as systolic and diastolic functions, are better than a non-vegan athlete's (47). Besides, a vegan athlete's end-diastolic volume and end-systolic volume are higher and stroke volume is lower than a non-vegan athlete. Measurable differences have not been seen between the muscle mass and bone density of vegan and non-vegan athletes (47). Vegan athletes have better cholesterol levels than non-vegan ones (48).

SOY PROTEIN CONSUMPTION AND CARDIOVASCULAR EFFECTS

Soy protein is a food frequently consumed by vegetarians rather than omnivores. The United States Food and Drug Administration authorized labeling of soy protein foods as reducing the risk of CVDs (49). However, it has not been definitively proven whether cholesterol efflux and macrovascular function can be changed with diets that are rich in polyphenols (50).

Soybeans contain many bioactive substances, including polyphenols and isoflavones (51). Flavonoids are grouped according to their chemical structure. These are: flavonols (quercetin, kaempferol), flavanols (catechins), flavones (apigenin), and isoflavones (daidzein, genistein) (51).

Many studies have observed that soy isoflavones reduce LDL levels, which has an important role in atherosclerosis pathogenesis (48, 52, 53). It has been found that blood cholesterol levels increase in many animals fed with animal protein diets (54, 55). Contrary, it has been demonstrated that using soy protein instead of animal protein causes hypercholesterolemia (48). In the studies on isoflavones, the bioactive molecule of soy, soy isoflavones caused arterial vasodilation and lower serum cholesterol in animals, and inhibit atherosclerosis in postmenopausal monkeys (56, 57). Some previous studies have been conducted to separate the protein effect from the isoflavone effect (53, 58-63). LDL cholesterol was reduced in two of these studies. It has been shown that protein influences LDL reduction and isoflavones have no effect (52, 63).

Cardiac complications due to radiotherapy include subacute or chronic CAD, congestive heart failure, ischemia, and myocardial infarction (64, 65). It is not enough to try to prevent interstitial fibrosis, inflammation of the myocardium, and thrombotic changes with anti-inflammatory and antithrombotic drugs (66). The inhibition of these radiation-induced damages with soy isoflavones has been proved histologically. It has been demonstrated that smooth muscle cell damage is reduced in the cardiac arteries of animals treated with radiotherapy and soy isoflavones (67). Soy isoflavones can be used as a complement to improve overall survival in patients surviving cancer with radiotherapy (67).

A prospective cohort study of Chinese women included nearly all soy foods - tofu, fried tofu, and tofu cakes. (68) The risk of cardiovascular disease, adjusted for age and energy, was reduced with soy protein intake (68). The elderly who consumed higher amounts of soy protein had a history of hypertension and a high body mass index. Women who consumed large amounts of soy protein had a lower risk of cardiovascular disease and a lower non-fatal myocardial infarction than women who consumed small amounts (68).

CONCLUSION

Studies in literature have generally shown that vegetarians have a lower risk of CVDs. Vegetarian diets contain low intakes of saturated fat and cholesterol. The consumption of food of animal origin is shown as a restrictive factor for choline, L-carnitine, betaine, trimethyl lysine levels. Therefore, the cardiovascular disease precursor TMAO is produced much less in the body. In addition, soy, which is consumed largely in vegetarian diets, is important for reducing the risk of CVDs. However, vegetarian diets can cause vitamin and mineral deficiencies since the diet does not contain animal products. Vitamin B deficiencies are especially important because vitamin B is responsible for homocysteine metabolism, and that plasma homocysteine concentration is one of the independent risk factors of CHD. For these reasons, it is important to regulate vegetarian diets by considering daily nutritional needs.

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CLINICAL AND HISTOPATHOLOGICAL EVALUATION OF EYELID LESIONS: RETROSPECTIVE ANALYSIS OF TERTIARY MEDICAL CENTER REFERRALS

Mustafa Ömer İzzettinoğlu[1], Fatih Erkan Akay[1], Rüveyde Garip[2]

[1]Trakya University School of Medicine, Edirne, TURKEY
[2]Department of Ophthalmology, Trakya University School of Medicine, Edirne, TURKEY

ABSTRACT

Aims: To clinically and histopathologically examine eyelid lesions and evaluate the consistency of clinical examination by comparing the provisional diagnoses of patients with their postoperative histopathology results. ***Methods:*** In this study, the records of 408 patients who applied to Trakya University, Department of Ophthalmology with an eyelid mass and underwent surgery between January 2000 to November 2019 were retrospectively analyzed. Patients' data comprised age, gender, location of the mass, lesion distribution according to age and gender, provisional clinical diagnosis of the patients, and histopathological reports. ***Results:*** Out of 408 patients, 220 (54%) were female, and 188 (46%) were male. The mean age of the patients was 46.9 ± 20.17 years (range; 5-90 years). In the histopathological examination of the lesions, 318 (77.9%) of them were benign, and 90 (22.1%) of them were malignant. The most common benign lesion was chalazion [112 (35.2%)], while the most common malignant lesion was basal cell carcinoma [71 (78.9%)]. The clinical pre-diagnosis and histopathological diagnosis were found to be compatible in 81 (90%) patients with a malignant lesion. There was a statistically significant difference in age between malignant and benign lesions, where malignant lesions were found more in older patients. The histopathological examination ended up being malignant in 2.2% of the lesions with a benign provisional diagnosis. ***Conclusion:*** In conclusion, even though most common eyelid lesions in our study were found to be benign, some lesions diagnosed as benign in clinic were found to be malignant after histopathological examination. Hence all excisions should be evaluated histopathologically to achieve a better clinical outcome in all patients with an eyelid lesion. ***Keywords:*** Eyelid, lesion, basal cell carcinoma, chalazion

INTRODUCTION

Eyelid lesions are common to come across in ophthalmology clinics (1). These lesions can be congenital, inflammatory, traumatic, or neoplastic (benign or malignant) (2). Eyelid lesions can be various lesions of benign or malignant tumors generated from all cutaneous layers, except for the subcutaneous fat tissue alongside benign lesions referring to the majority percentage of all lesions (2, 3). Provisional diagnoses are made by clinical inspection using routine ophthalmologic practices and findings from the examination are verified by histopathological investigations (2). Inadequate and late diagnoses cause more risk for the patients and require more invasive surgeries, which usually end up with worse results (4, 5). Early diagnoses for malignant lesions especially happen to have high importance in the management of lesions through earlier treatment.

The incidence of eyelid lesions varies by genetic and environmental factors such as sunlight and ultraviolet radiation (6). Therefore, the distribution data of various lesions' locations are highly important for an ophthalmologist for the discrimination of the malignancies.

There are very few studies emphasizing the competence and importance of the provisional diagnoses approved with histopathological reports despite the existence of various studies evaluating demographical and histopathological features of eyelid lesions in our country. This study aims to evaluate the clinical, demographical, and histopathological features of eyelid lesions and the accuracy of provisional diagnoses and compare early diagnoses with histopathological reports.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2020/425). In this retrospective cross-sectional study, the data of 408 patients with an eyelid mass who were admitted to the tertiary ophthalmology clinic of Trakya University Hospital between January 2000 and November 2019 were evaluated retrospectively by histopathologically examining the materials of the patients that were obtained from mass excision. The study was carried out under the tenets of the Declaration of Helsinki. The written consent for the use of medical information of patients was also received from all of the participants or parents/guardians of the minors.

Demographic data such as patient's age and gender, location of the mass, lesion distribution according to age and gender, provisional clinical diagnosis of the patients, and histopathological reports were obtained from the medical records of the patients.

Address for Correspondence: Mustafa Ömer İzzettinoğlu, Trakya University School of Medicine, Edirne, TURKEY
e-mail: omer.iz@icloud.com
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ORCID iDs of the authors: MÖİ: 0000-0001-6736-7294; FEA: 0000-0001-7598-1016; RG: 0000-0003-2235-9017.

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Patients who were admitted to the ophthalmology department with the complaint of eyelid mass met the inclusion criteria. Patients with ophthalmological masses located in areas other than the eyelid were excluded from this study.

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

RESULTS

In the present study, 220 (54%) female, and 188 (46%) male patients made up the total number of 408 patients. The mean age of the patients was 46.9 ± 20.17 years (range; from 5 to 90 years). Two hundred and twelve (51.9%) patients had left eye involvement whereas 196 (48.1%) patients had right eye involvement. The distribution of the lesions according to histopathological diagnoses, locations, and demographic features are presented in Table 1.

Ninety-five patients had a malignant provisional diagnosis, however, after histopathological analysis, only 81 of them were proved to have one. It was revealed that the detection rate with clinical examination was at 90%. It was seen that 9 (2.2%) out of

Table 1: Summary statistics for location, and demographic parameters of eyelid lesions according to benignancy and malignancy.

	Benign Eyelid Lesions	*Malignant Eyelid Lesions*	*Total*	*P-value*
Number of patients [n (%)]	318 (77.9)	90 (22.1)	408 (100)	
Gender [n (%)]				<0.242
Female	178 (55.9)	43 (47.8)	221 (100)	
Male	140 (44.1)	47 (52.2)	187 (100)	
Age*	41.67 ± 18.74	64.52 ± 13.10		***0.001***
Location [n (%)]				
Upper eyelid	181 (56.9)	22 (24.4)	203 (50.7)	
Lower eyelid	110 (34.6)	48 (53.3)	158 (38.7)	
Medial epicanthus	19 (6)	15 (16.7)	34 (8.1)	
Lateral epicanthus	8 (2.5)	5 (5.6)	13 (2.5)	

**Data were expressed as mean ± standard deviation.*
Statistically significant value is marked in bold.

Table 2: Summary statistics for histopathological diagnoses, location, and demographic parameters of benign eyelid lesions.

Histopathological Diagnoses	*Number of Patients [n (%)]*	*Gender (Female/Male)*	*Age**	*Location*
Chalazion	114 (27.94)	59/53	32.88 ± 18.14	UE 58.0%
Squamous papilloma	43 (10.54)	21/22	51.26 ± 14.20	UE 58.1%
Epidermal cyst	28 (6.86)	15/13	52.46 ± 15.42	UE 53.8%
Seborrheic keratosis	22 (5.39)	9/13	58.10 ± 16.89	UE 45%
Xanthelasma	22 (5.39)	13/9	45.33 ± 6.71	UE 100%
Cysts of Moll and Zeiss	20 (4.9)	14/6	39.94 ± 4.88	LE 58.8%
Nevus	18 (4.41)	13/5	46.75 ± 7.84	UE 83.3%
Verruca vulgaris	14 (3.43)	9/5	45.40 ± 19.01	UE 80%
Dermoid/epidermoid cyst	12 (2.94)	2/10	47 ± 4.24	UE 83.3%
Capillary hemangioma	10 (2.45)	10/0	39.40 ± 24.35	UE = LE
Keratoacanthoma	6 (1.47)	3/3	51.67 ± 15.67	LE 66.7%
Cutaneous horn	5 (1.23)	5/0	37.20 ± 12.73	UE 60.0%
Xanthogranuloma	2 (0.49)	1/1	45 ± 7.12	UE = LE
Trichoepithelioma	2 (0.49)	1/1	63 ± 22.62	UE = LE
Apocrine hidrocystoma	1 (0.25)	1/0	50	LEC

***UE:** Upper eyelid, **LE:** Lower eyelid, **LEC:** Lateral epicanthus*
**Data were expressed as mean ± standard deviation.*

Table 3: Summary statistics for histopathological diagnoses, location, and demographic parameters of malignant eyelid lesions.

Histopathological Diagnoses	*Number of Patients [n (%)]*	*Gender (Female/Male)*	*Age**	*Location (%)*
Basal cell carcinoma	71 (17.40)	35/36	64.34 ± 13.22	LE 60.6%
Squamous cell carcinoma	14 (3.43)	4/10	64.13 ± 13.23	UE = LE (40% each)
Sebaceous gland carcinoma	3 (0.74)	2/1	65 ± 14.10	UE 66.7%
Malignant melanoma	2 (0.49)	2/0	74 ± 2.82	UE = MEC

***LE:** Lower eyelid, **UE:** Upper eyelid, **MEC:** Medical epicanthus*
**Data were expressed as mean ± standard deviation.*

313 clinically benign lesions were histopathologically diagnosed as malignant lesions. 14 cases were suspected to be malignant lesions but histopathologically diagnosed as benign lesions. It was revealed that clinical pre-diagnosis of 304 (97.1%) benign lesion cases was concordant with the histopathological reports. In addition, as for basal cell carcinoma (BCC) cases, it was seen that lower eyelid was the most common location yet there were 2 cases of BCC on lateral epicanthus (2.8%). It was found that the correct clinical diagnosis rate of cases such as seborrheic keratosis, keratoacanthoma, and intradermal nevus was relatively low whereas the clinical diagnosis accuracy of cases such as chalazion, xanthelasma, squamous papilloma, Moll and Zeiss cysts were high. The distribution of the lesions according to histopathological diagnoses and the demographic features are presented in Tables 2 and 3.

DISCUSSION

Eyelid lesions are frequent occurrences in the daily practice of practitioners. Fortunately, even though some lesions may have findings of potential malignancy, they usually happen to be benign (2). Additionally, studies have revealed the incidence ratio of benign lesions ranges from 68.8% to 95% (4-9). In our study, this ratio was found to be 77.9%, which is relatively lower compared to other studies that had larger sample sizes (4, 8). Alongside the differences in genetic and environmental factors, the difference in results could be attributed to cases that were pre-diagnosed with a malignant lesion who were then referred to a tertiary health care facility.

According to the literature, eyelid tumors are prone to be located on the lower eyelid followed by the upper eyelid, medial, and lateral epicanthus (8). Furthermore, it was indicated that the benign lesions are located more on the upper eyelid whereas malignant lesions are located more on the lower eyelid (4, 7, 8). Our results were in line with the current literature. The reason for the number of malignant lesions being high on the lower eyelid is due to BCC being common in the population (5).

In our study, it was revealed that benign lesions occurred more commonly on female patients [178 (55.9%)], and the malignant lesions on male patients [47 (52.2%)]. A similar study by Coroi et al. (8), which was conducted with 471 cases, demonstrated that malignant lesions are more common in male patients. Moreover, the study of Huang et al. (4) supported the results of malignant lesions being more frequent on male patients with a ratio of 63.4%. Additionally, the study revealed that the benign lesion features had no difference in location regarding gender (4). Malignant lesions are reported to occur at relatively older ages compared to benign lesions (4, 6, 8, 10). In our study, malignant lesions were found in patients of older ages, which is concordant with the literature.

In the present study, chalazion [114 (27.94%)] was the most common benign lesion followed in order by squamous papilloma [43 (10.54%)], epidermal cyst [28 (6.86%)], seborrheic keratosis [22 (5.39%)], and xanthelasma [22 (5.39%)]. In a study that was conducted by Al-Faky (2), it was reported that the most common benign lesion was apocrine hidrocystoma, followed by chalazion, verruca, epidermal cyst, nevus, seborrheic keratosis, and xanthelasma. According to the study of Gundogan et al. (1), the five most common benign lesions were squamous papilloma, melanocytic nevus, seborrheic keratosis, epidermal cyst, and apocrine hidrocystoma. Chalazion was found as the most common benign lesion in the present study, whereas it was low in frequency in other studies. Diversity of the patient population who are admitted to health care centers, along with the difference in geography, could account for the dissimilarity in frequencies of eyelid lesions.

In previous studies, BCC was reported to be one of the most common malignant eyelid tumors (4, 6, 8, 10). On the other hand, according to studies conducted in Asia, squamous cell carcinoma (SCC) has a similar incidence as BCC, if not more common (11-13). In studies that were based in Turkey, it was reported that BCC was the most common malignant tumor of eyelids, whereas SCC was the second most common (1, 5, 7, 9, 14). BCC is mostly located in the lower eyelid (12). In the present study, BCC was mostly on the lower eyelid, and quite rarely lateral canthus, which is concordant with the basic knowledge of literature (12, 13). According to a study that was carried out in India by Kaliki et al. (13), 59% of the SCC cases had an upper eyelid involvement. On the contrary, in our study, SCC was located in the upper and lower eyelids equally. It is postulated that SCC is located more in the upper eyelid due to the abundant meibomian glands the upper eyelid contains (10).

It was shown that 2.2% of the cases that were clinically pre-diagnosed with benign lesions turned out to have malignant lesions according to histopathological reports. In the study of Kersten et al. (15), this rate was reported to be at 1.9%. In a study by Uzlu et al. (7), 4.7% of cases clinically pre-diagnosed with benign lesions were reported as premalignant, and 5.9% of cases were reported as malignant according to histopathological reports. In the present study, 3 cases that were evaluated as chalazion were later diagnosed as SCC after histopathological analyses. 2 malignant melanoma cases were evaluated as nevus. The high rate of inconsistency in incorrect diagnoses is considered to happen due to some lesions not taking place on a pre-diagnosis list because of their low occurrence; for instance, SCC could be confused with chronic blepharitis, especially at early stages. Keratoacanthoma and seborrheic keratosis are especially clinically evaluated as malignant lesions. Relatively less common eyelid lesions are significantly low in the accuracy of clinical diagnosis.

In the present study, demographic, and histopathological features of eyelid lesions in Turkey were evaluated. There are many studies regarding this topic in Turkey, and this study is a research article that evaluates the accuracy of recent clinical examinations. The most important limitation of this study was having a lower number of cases with rare eyelid lesions. Another limitation was that this study was conducted retrospectively.

In conclusion, specialists could come across malignant lesions that can be evaluated as benign due to the fact that benign lesions of the eyelid are highly common. Therefore, the possibility of malignant lesions on patients who were pre-diagnosed clinically with benign tumors should be taken into account and detailed examination and histopathological investigations should be performed on the patients. Early diagnosis and surgical excisions of malignant lesions provide better management, save the patients from more complicated surgeries, and maintain more successful cosmetic results.

Ethics Committee Approval: This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2020/425).
Informed Consent: Informed consent was obtained from all of the subjects.
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THE EFFECTS OF ACYCLOVIR ON ANGIOGENESIS IN CHICK CHORIOALLANTOIC MEMBRANE MODEL

İbrahim Kılıççalan, Bekir Nihat Doğrul, Abdulbaki Erkovan, Ekrem Samet Aşçı

Gülhane School of Medicine, University of Health Sciences, Ankara, TURKEY

ABSTRACT

Aims: This study aims to reveal the effects of acyclovir on angiogenesis and to assess the experimental doses. ***Methods:*** In the study, the chick chorioallantoic membrane model was used as an experimental model. Forty fertilized eggs were kept at 85-90% relative humidity, below 37°C until the fifth day post-fertilization, when the vessels in the chick chorioallantoic membrane model appeared and the drugs were applied. Four different concentrations of acyclovir were chosen to determine the mode of action and dose dependence: 3.55 mg/mL, 7.1 mg/mL, 14.2 mg/mL, and 28.4 mg/mL. Each of the 1 mL total acyclovir concentrations were applied to the chick chorioallantoic membrane surfaces. The chick chorioallantoic membranes treated with sterile distilled water were designated as controls. Eight eggs were used for each test group. After applying the drug, all the eggs were covered with transparent tape and kept under the same conditions throughout the experiment. The results were evaluated 48 hours after the drugs were administered and the results were recorded with a digital camera. ***Results:*** In our study, it was observed that 3.55 mg/mL acyclovir concentration shows the reduced density of capillaries around the pellet and no change in the number of capillaries. Both 7.1 mg/mL and 14.2 mg/mL concentrations of acyclovir caused a local reaction that was restricted to the membrane and it was attributed to local crystallization reaction. The concentration of 28.4 mg/mL had a toxic effect on the eggs. ***Conclusion:*** In this study, it was found that acyclovir has a very weak anti-angiogenic effect dose-dependently at the concentrations used. Considering that an observational model was used in our study, quantitative studies are needed for assessing anti-angiogenic effects in the future. There is also a need for further studies to elucidate the effects of acyclovir on vascular endothelial growth factor level and which stage of the angiogenesis-related process it is specifically effective on. ***Keywords:*** Angiogenesis, acyclovir, chorioallantoic membrane, endothelial cells

INTRODUCTION

Acyclovir (acycloguanosine) is an antiviral drug that inhibits DNA synthesis and viral replication. In doing so, its toxicity to host cells is low, and its concentration in herpes simplex virus (HSV)-infected cells are 40-100 times higher than in normal cells (1, 2). Acyclovir is available in oral, topical, and intravenous forms. It is used for HSV-1, HSV-2, and varicella-zoster virus (VZV) infections that can cause herpetic keratitis, herpetic encephalitis, and genital herpes (3, 4). Acyclovir is still the gold standard treatment today for HSV infections (5). In addition to treatment, acyclovir prophylaxis also plays an important role in medicine (6, 7). However, it has been shown in the literature that acyclovir acts by increasing apoptosis in some cancer lines (8, 9). This situation paves the way for studies on the use of acyclovir in different treatment protocols.

Angiogenesis is defined as the formation of new capillaries from existing capillaries. It plays a role in many physiological processes such as wound healing, growth, and development of organs, and takes a part in pathological processes like cancer development. Chick chorioallantoic membrane (CAM) assay is an experimental model that is generally used to study in vivo angiogenesis, tumor cell invasion, and metastasis (10).

As an antiviral drug, acyclovir has been studied in other areas besides HSV and VZV. However, studies investigating its effect on angiogenesis are insufficient. In this study, we aim to examine the effect of acyclovir on angiogenesis using the chick CAM model with four different concentrations.

MATERIAL AND METHODS

The CAM model was used in our study. CAM model is frequently used in studies due to its low cost, easy use, and real-time visualization of the model (11). In our study, 40 fertilized eggs of chicken were purchased from a poultry institute in Ankara, Turkey. Eggs were kept in an incubator at 37 °C and 85-90% relative humidity for five days before drug application. Incubated eggs were confirmed after vascularization appeared on CAM. To open a small window in the egg, the upper part of the eggshell is peeled without damaging the embryonic structures. Acyclovir (Zovirax 250 mg; GlaxoSmithKline) for intravenous administration was diluted with distilled water. Four different concentrations of acyclovir were chosen to determine the effectiveness, dose-dependency, and toxicity.

In human pharmacokinetic studies, when acyclovir (Zovirax) was administered at a dose of 5 mg/kg, its Cssmax was 9.8 mcg/mL, its Csstrough was 0.7 mcg/mL; when administered at a dose of 10 mg/kg, its Cssmax was found to be 22.9 mcg/mL, and its Csstrough as 1.9 mcg/mL according to the United States Food and Drug Administration (12). Doses were determined in the study to cover the therapeutic range in humans. For this purpose, acyclovir was administered to the eggs at concentrations of 3.55 mg/mL,

Address for Correspondence: İbrahim Kılıççalan, Gülhane School of Medicine, University of Health Sciences, Ankara, TURKEY
e-mail: ibrahimklccalan@gmail.com
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ORCID iDs of the authors: İK: 0000-0001-7086-4988; BND: 0000-0001-7498-8507; AE: 0000-0002-5043-9703; ESA: 0000-0003-0412-5743.

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7.1 mg/mL, 14.2 mg/mL and 28.4 mg/mL, respectively. Eight eggs were used for each test group. 50 µL aliquots of 1 mL total acyclovir concentrations were applied to the CAM surfaces. The control group was treated with distilled water only. After applying acyclovir, all the eggs were covered with paraffin film to prevent dehydration and placed back in the incubator. All eggs were kept under the same conditions throughout the experiment.

The results were evaluated 48 hours after the medications were administered, as advised by standard CAM experiment protocols (11). Visualization of blood vessels was recorded with a digital camera (Konica Minolta, Tokyo, Japan). The reduced density of capillaries around the drug application area was considered as an indicator of the anti-angiogenic effect (13, 14). A scoring system used in many previous studies was used to evaluate the anti-angiogenic effects (Table 1) (15, 16).

Table 1: Scoring system for the evaluation of the anti-angiogenic effects on chick chorioallantoic membrane model (15, 16).

Score	*Effects observed*
0: No effect	-None
0.5: Very weak effect	-No capillary-free area
	-Area with reduced density of capillaries around the pellet not larger than the area of the pellet
1: Weak to medium effect	-Small capillary-free area or area with significantly reduced density of capillaries
	-Effects not larger than double the size of the pellet
2: Strong effect	-Capillary-free area around the pellet at least double the size of the pellet

RESULTS

Two days after the application of acyclovir solutions, the vascular network of the treated area of the membrane presented several macroscopic changes compared to the untreated areas of egg membrane, as untreated areas can be observed in Figure 1.

In the area applied at the concentration of 3.55 mg/mL, there was reduced macroscopic density, and no increase in the number of capillaries was observed (Figure 2). Physiological angiogenesis was observed in the areas where acyclovir was not applied. This observation was assessed on a score of 0 to 0.5 which means a very weak anti-angiogenic effect (Table 1). At the concentrations of 7.1 mg/mL and 14.2 mg/mL, we were unable to interpret any anti-angiogenic or angiogenic effects due to local reaction (Figure 3, Figure 4).

A toxic effect was detected in the application area with surrounding vascular structure at the concentration of 28.4 mg/mL (Figure 5). It was concluded that the concentration of 28.4 mg/mL acyclovir is the toxic dose to eggs because all eight eggs treated with 28.4 mg/mL showed global toxic effects as the membrane structures were destroyed.

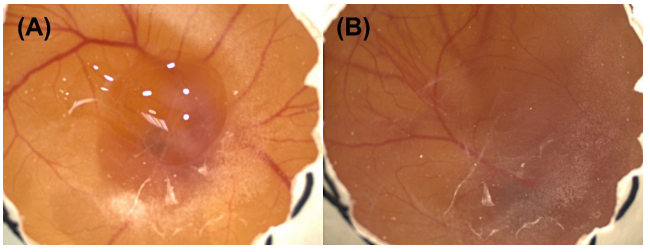

Figure 1: Images of capillary plexus of the CAM treated with sterile distilled water. A: Image recorded at day 0 (five-day-old chick embryo). B: Image recorded after the administration of the sterile distilled water as a control (seven-day-old chick embryo).

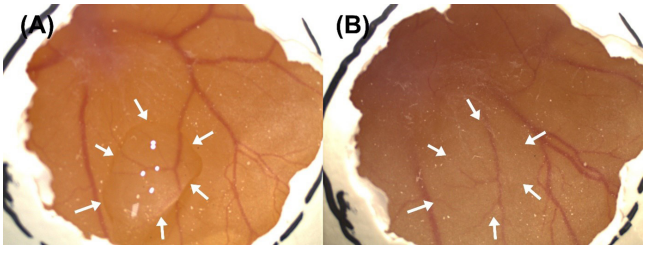

Figure 2: Images of capillary plexus of the CAM treated with 3.55 mg/mL. A: Image recorded at day 0 (five-day-old chick embryo). (The white arrows show the boundaries of the area affected by the applied substance.) B: Image recorded after the administration of the drug (seven-day-old chick embryo). Minimal to moderate reduced density of capillary can be seen. But the other areas other than pellet shows physiologic angiogenesis with increased density of capillaries and sprouting of vessels (The white arrows show the boundaries of the area affected by the applied substance).

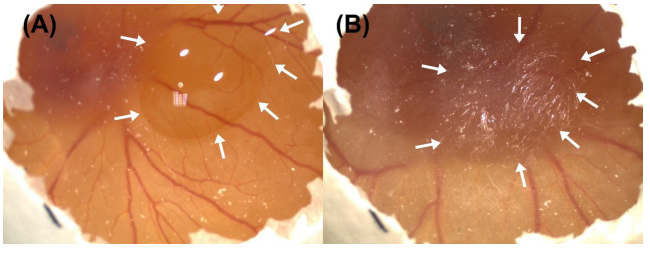

Figure 3: Images of capillary plexus of the CAM treated with 7.1 mg/mL. A: Image recorded at day 0 (five-day-old chick embryo). (The white arrows show the boundaries of the area affected by the applied substance.) B: Image recorded after the administration of the drug (seven-day-old chick embryo). The local crystallization reaction made observational evaluation difficult (The white arrows show the boundaries of the area affected by the applied substance).

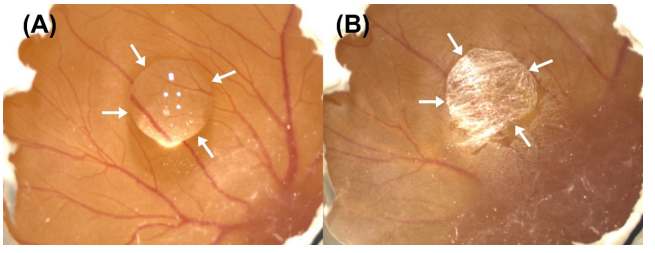

Figure 4: Images of capillary plexus of the CAM treated with 14.2 mg/mL. A: Image recorded at day 0 (five-day-old chick embryo). (The white arrows show the boundaries of the area affected by the applied substance.) B: Image recorded after the administration of the drug (seven-day-old chick embryo). The local crystallization reaction made observational evaluation difficult (The white arrows show the boundaries of the area affected by the applied substance).

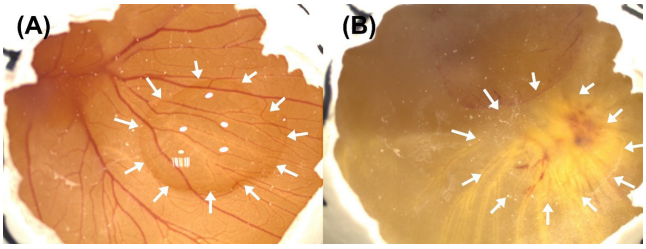

Figure 5: Images of capillary plexus of chick CAM treated with 28.4 mg/mL. A: Image recorded at day 0 (five-day-old chick embryo). (The white arrows show the boundaries of the area affected by the applied substance.) B: Image recorded after the administration of the drug (seven-day-old chick embryo). Global toxicity can be seen (The white arrows show the boundaries of the area affected by the applied substance).

DISCUSSION

Angiogenesis is the generation of new vessels from existing vessels. It occurs physiologically or pathologically in the body (17). CAM is a simple and in vivo model that is suitable for showing whether a substance is angiogenic or anti-angiogenic. Being able to perform the assay and make an observation by directly accessing the membrane is one of the advantages of the CAM model, but also it is more physiological than in vitro models (18). Besides its simplicity, it is a great advantage of the CAM study that the fertilized egg does not require ethical approval until it reaches 14 or 17 days of development in most countries (19). However, quantification of angiogenesis is usually not easy as it is based on visual observation.

Acyclovir is an antiviral drug used in HSV-1, HSV-2, and VZV infections (3, 4). However, publications show that acyclovir has an antiproliferative effect in cancers, such as breast cancer, leukemia, and glioblastoma multiforme (8, 9, 20). In the study by Shaimerdenova et al. (8), it was found that acyclovir decreased cell proliferation and increased apoptosis in the MCF7 breast cancer cell line. Due to this feature, it has been stated that acyclovir can be used in the treatment of breast cancer. In the study of Benedetti et al. (9) on leukemia cell lines, it was determined that acyclovir increased apoptosis in Jurkat (acute T-cell leukemia), U937, and K562 leukemia cell lines, and it was stated that it could be used together with chemotherapeutic drugs in the treatment. In the study of Kominsky et al. (20), it was revealed that the antiproliferative effect of acyclovir in glioblastoma multiforme cell lines is higher than in normal human astrocyte cell lines. Based on these studies, it was investigated whether acyclovir has an effect on angiogenesis in tumor cells. In the literature review, Lu et al. (21) found that acyclovir decreased the expression level of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in mouse renal cells. Even though there are studies investigating acyclovir's effects on cancer cell lines as discussed above, there has been a lack of studies conducted in current literature investigating the effect of acyclovir on angiogenesis (22, 23). From this point of view, we examined the effect of acyclovir on angiogenesis in the CAM model. In our study, acyclovir was applied at different concentrations. As a result of the experiment, toxic effects were observed in CAM models administered at 28.4 mg/mL, while very weak anti-angiogenic effects were observed at a concentration of 3.55 mg/mL. The crystallized membranes observed at the concentration of 7.1 mg/mL and 14.2 mg/mL have been attributed to local crystallization reaction, which is also a well-known side effect of acyclovir, mentioned in literature as acyclovir induced crystal nephropathy (24). The local hyperosmotic reaction is a known disadvantage of the CAM model. It is known that certain substances in the form of salt crystals can cause hyperosmotic damage to the CAM membrane (25). It should be remembered that this reaction may occur in further CAM studies with acyclovir, and the assay should be planned accordingly.

The limitations of our study were that the study was conducted in an observational model and therefore its effect on angiogenesis was not examined with quantitative methods or at the gene level. However, a scoring system was used regarding the very weak anti-angiogenic effect of acyclovir (Table 1). Also, the anti-angiogenic effect needs to be confirmed by conducting studies on factors such as vascular endothelial growth factor gene level, or in vitro cell culture models as well as in vivo models (24).

We recommend that those who will study acyclovir on the CAM model in the future uses doses less than 7.1 mg/mL due to both the local non-specific reactions of the CAM model and the known crystallization reaction of acyclovir. In addition, increasing the number of eggs used in CAM experiments between 3.55 mg/mL and 7.1 mg/mL acyclovir doses will facilitate the observational evaluation of the study. On a further note, the amount of the systemically administered dose of acyclovir reaching the area where the corresponding tissue is located will be responsible for the targeted antiangiogenic effect in cancer treatments. The amount of the administered dose does not reach this area completely. Therefore, the doses administered in this study are not necessarily the doses for the antiangiogenic effect in humans, they correspond to higher doses in this study. These doses should be assessed in microgram/mL to further understand the therapeutic concentrations reaching the exact affected area for humans.

In conclusion, we observed very weak anti-angiogenic effects of acyclovir on the CAM model at a concentration level. It is known that anti-angiogenic agents can cause positive effects by disrupting tumor neovascularization (26). Some publications concluded that acyclovir has an antiproliferative effect on breast cancer, leukemia, and glioblastoma multiforme (8, 9, 20). Extensive studies are needed on whether acyclovir can be used as adjuvant therapy in cancer treatment. Further studies are also needed to study the different potential effects of acyclovir on angiogenesis and perform quantitative analysis.

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LONG-TERM SURGICAL OUTCOMES OF PATIENTS WITH PHACOMORPHIC GLAUCOMA

Mustafa Ömer İzzettinoğlu[1], Ayça Küpeli Çınar[2], Rüveyde Garip[2]

[1]Trakya University School of Medicine, Edirne, TURKEY
[2]Department of Ophthalmology, Trakya University School of Medicine, Edirne, TURKEY

ABSTRACT

Aims: To retrospectively analyze clinical characteristics of patients diagnosed with phacomorphic glaucoma in the Ophthalmology Department of Trakya University Hospital. ***Methods:*** This retrospective cross-sectional study was conducted with patients who were diagnosed with phacomorphic glaucoma in the Ophthalmology Department of Trakya University Hospital between January 2010 and January 2021. ***Results:*** Initially, 19 eyes from 19 patients diagnosed with phacomorphic glaucoma met the inclusion criteria. The mean preoperative best-corrected visual acuity was 0.1 ± 0.3 Snellen visual acuity (ranging from 0.001 to 1.0 Snellen visual acuity). A statistically significant increase in postoperative best-corrected visual acuity during the follow-ups has been observed. In terms of intraocular pressure levels, patients had mean preoperative 32.3 ± 11.2 mmHg (range:15-55 mmHg). The decrease in postoperative intraocular pressure levels during follow-ups was statistically significant. ***Conclusion:*** Lens removal through phacoemulsification or intracapsular cataract extraction is an effective and safe procedure in the treatment of phacomorphic glaucoma, ensuring a satisfactory long-term intraocular pressure control and a rapid functional recovery. However, most of the patients are expected to have an outcome of favorable best-corrected visual acuity after surgery in the long term. ***Keywords:*** Cataract, phacomorphic glaucoma, epidemiology, glaucoma

INTRODUCTION

Phacomorphic glaucoma (PG) is secondary angle-closure glaucoma that results from mature cataract formation. The narrowing of the angle between the iris and the cornea could occur slowly with cataract formation by a forward push of the iris or acute precipitation by an intumescent cataractous lens which leads to obstruction of aqueous flow between the border of the anterior capsule of the lens and the pupil (1, 2). The three main causes of blindness have been reported to be cataract, trachoma, and glaucoma; together accounting for two-thirds (71%) of all blindness (3). Cataract has been reported to be the single largest cause of bilateral blindness (15.83 million) on a global scale, and the backlog of unoperated cataract cases have exceeded the number that was estimated in 1990 by World Health Organization Consultation (3). PG happens to be more common in developing countries due to the lack of awareness of cataracts as a disease and delayed lens extraction operations (4).

The risk factors for PG were determined to be age being greater than 60 years, shallow anterior chamber, and axial length shorter than 23.7 mm (5). The patients with PG mostly present to the clinics with pain in the eye, a history of decreased vision, evidence of mature cataract formation, angle-closure, and elevated intraocular pressure (IOP) in the affected eye. The presence of an intumescent cataractous lens and the presence of cell and flare essentially play the biggest role in the distinction between primary angle-closure glaucoma and phacomorphic angle-closure glaucoma (1).

Initial PG therapy includes medical treatment such as topical prostaglandins, carbonic anhydrase inhibitors, beta-blockers, and hyperosmotic agents such as intravenous mannitol or oral glycerin. An ophthalmology specialist should use parasympathomimetic agents with caution since these agents can cause pupillary blockage. If the medical treatment alone is not enough to control the IOP, laser iridotomy is usually performed and other options include corneal depression with a Zeiss 4-mirror lens. If the eye with no symptoms is also predisposed to angle-closure glaucoma, prophylactic laser iridotomy is suggested to be performed on the fellow eye (1, 2). Cataract extraction is the definitive treatment of PG (1). It is highly important to raise awareness on cataracts and the outcomes of the disease to recognize the patients with PG as early as possible and apply the correct ophthalmological procedures when PG is detected.

This retrospective study aims to analyze the clinical characteristics, examination findings, and outcomes of the patients diagnosed with PG in the tertiary ophthalmology clinic of Trakya University Hospital.

MATERIAL AND METHODS

This retrospective cross-sectional study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2021/115). The study was carried out in accordance with the tenets of the Declaration of Helsinki. Written informed consent for the use of medical information of patients was also received from all of the participants.

Our study analyzed 19 eyes of 19 patients who were diagnosed with PG and whom the cataract extraction surgery was performed in the Ophthalmology Department of Trakya University Hospital between January 2010 and January 2021. Demographic data such

Address for Correspondence: Mustafa Ömer İzzettinoğlu, Trakya University School of Medicine, Edirne, TURKEY
e-mail: omer.iz@icloud.com
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Available at https://tmsj.trakya.edu.tr

ORCID iDs of the authors: MÖİ: 0000-0001-6736-7294; AKÇ: 0000-0003-4495-9603; RG: 0000-0003-2235-9017.

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as age and gender, duration of symptoms, accompanying systemic comorbidities such as hypertension, diabetes, the usage of topical prostaglandins, beta-blockers, carbonic anhydrase inhibitors, and alpha agonists, and initial and following clinical findings were obtained from the medical records of the patients. All patients underwent complete ophthalmologic examination at each visit including best-corrected visual acuity (BCVA) determined by Snellen chart, anterior segment biomicroscopic examination, IOP measurement with Goldmann applanation tonometer, and detailed fundus examination obtained with 78-diopters non-contact lens.

Individuals diagnosed with PG were included in this study. The ones who have underlying corneal pathologies, ocular-vascular diseases (central retinal artery occlusion, retinal venous occlusion), accompanying macular pathologies like a macular hole and macular degeneration that could lead to unreliable examinational results were excluded from the study.

The following findings were documented at the initial visit: BCVA, IOP, ocular comorbidities such as central retinal vein occlusion, pseudoexfoliation syndrome, and presence of glaucoma.

The following findings were documented at the follow-up visits: performed surgical technique of cataract extraction, the usage and the duration of the usage of topical anti-glaucomatous agents, kinds of anti-glaucomatous agents that have been used, measurements of BCVA and IOP of the postoperative first day, first week, first month, and the third month, and the presence of postoperative complications.

Surgical success was determined when postoperative IOP decrease and postoperative BCVA increase were achieved. In the present study, postoperative IOP less than 20 mmHg and one decimal increase in the Snellen line in terms of BCVA were considered surgical achievements.

Statistical Analysis

The collected data were analyzed statistically by using IBM SPSS Statistic 20 for Windows (Version 20.0. Armonk, NY: IBM Corp.). Mean and standard deviation values were calculated using descriptive statistical measures. The frequency distribution of qualitative data was quantified in percentages. The Chi-square test was used for qualitative comparison. Normality distribution of the data was evaluated with the Shapiro-Wilk test. Quantitative data were compared with the Student t-test. Friedman test was used to compare repeated measures more than 2 in quantity when normal distribution was rejected. Patients with negative light perception were not included in the statistical analysis. P-value of <0.05 was considered to be statistically significant.

RESULTS

Initially, 19 eyes from 19 patients with the diagnosis of PG met the inclusion criteria. Eleven (57.9%) patients were female, and 8 (42.1%) patients were male. The summary of patients' characteristics including mean age, mean duration of symptoms, gender, number of the affected eye and its side, and used topical anti-glaucomatous agents are presented in Table 1.

Five (26.3%) patients were under the usage of carbonic anhydrase inhibitor, six (31.6%) patients received beta-blockers. Eight (42.1%) patients received phacoemulsification and eleven (57.9%) patients underwent intracapsular cataract extraction surgery.

The mean preoperative BCVA was 0.1 ± 0.3 Snellen visual acuity (ranging from 0.001 to 1.0 Snellen visual acuity). Statistically significant increase in postoperative BCVA during the follow-ups has been observed (p<0.001, Friedman test).

In terms of IOP levels, patients had a mean preoperative IOP of 32.3 ± 11.2 mmHg (ranging from 15 to 55 mmHg). The decrease in postoperative IOP levels during follow-ups was statistically significant (p<0.001, Friedman test). All patients had postoperative third-month IOP levels less than 20 mmHg.

In terms of postoperative complications, 9 (47.4%) patients had corneal edema, 4 (21.1%) patients had Descemet folds, 2 (10.5%) patients had hyphema, 1 (5.3%) patient had pupillary blasted exudation, and 3 (15.8%) patients had no complications at all. Detailed and precise information of all patients in this study conducted with a small number of patients in terms of BCVA and IOP are shown in Table 2 to give a better perspective on the prognosis of the patients.

Table 1: Patient characteristics.

	Number of Patients [n (%)]
Age (years)*	78.2 ± 7.9 (53-88)
Duration of Symptoms (days)*	64.6 ± 115.4 (1-365)
Gender	
Female	11 (57.9)
Male	8 (42.1)
Eye Side	
Right	10 (52.6)
Left	9 (47.4)
Topical anti-Glaucomatous Agent	
CAI	5 (26.3)
Beta Blocker	6 (31.6)
None	8 (42.1)

CAI: *Carbonic anhydrase inhibitor*
**Data were expressed as mean ± SD (min-max).*

Table 2: Preoperative and postoperative BCVA in Snellen decimal of all patients.

Patient Number	*Pre-op*	*Post-op Day 1*	*Post-op Week 1*	*Post-op Month 1*	*Post-op Month 3*
1	0.0010	0.0300	0.10	0.20	0.40
2	0.0010	0.0010	0.0010	0.0500	0.0500
3	0.0010	0.0050	0.0300	0.10	0.20
4	0.60	0.20	0.70	0.0500	0.60
5	0	0	0	0	0
6	0.0001	0.0010	0.0010	0.0010	0.0010
7	0.0160	0.0010	0.0160	0.20	0.0010
8	0	0	0	0	0
9	1	0.0030	0.30	0.50	0.70
10	0.0010	0.0010	0.30	0.40	0.70
11	0.0001	0.0001	0.0001	0.0001	0
12	0.0001	0.0010	0.0010	0.0300	1
13	0.0010	0.0010	0.0010	0.0010	0.0010
14	0.0010	0.0160	0.20	0.70	0.70
15	0.0001	0.0010	0.40	0.60	0.0010
16	0	0	0	0	0.70
17	0.0010	0.0010	0.0080	0.10	0.0160
18	0.0010	0.0010	0.0010	0.0300	0.10
19	0.0001	0.0010	0.0500	0.0500	0.0500
Mean ± Standard Deviation	0.10 ± 0.25	0.02 ± 0.44	0.13 ± 0.19	0.19 ± 0.22	0.28 ± 0.33
Median	0.001	0.001	0.008	0.050	0.050
Maximum	1	0.20	0.70	0.70	1
Minimum	0	0	0	0	0

BCVA: *Best-corrected visual acuity,* ***Pre-op:*** *Preoperative,* ***Post-op:*** *Postoperative*

DISCUSSION

Cataract is known to be the most important cause of blindness in developing countries, mostly occurring in elder rural populations (6). Unoperated cataractous lenses eventually lead to major complications of PG causing poor vision and high IOP. This delay of lens extraction mostly happens due to the lack of awareness about the significance of early cataract management in developing countries (6). PG is secondary angle-closure glaucoma which is resulted from mature cataract formation. With a forward push of the iris or acute precipitations of the intumescent cataractous lens, narrowing of the angle leads to high IOP levels (7).

Phacomorphic glaucoma mostly occurs in elderly patients with delayed lens extraction and rarely in the young population with a genetically large lens (7). In the present detailed study, it was revealed that the range of the age of patients with PG was at the range of 53-88 years with the mean age of 78.2 years, which was consistent with the findings of other studies (6, 7). Regarding gender, female patients are predominant to PG according to the present study. Demographic data of other studies have also shown similar results of females making up the majority of the total group with PG (6-8). The predominance of females to have PG is thought to exist due to the socioeconomic repression and the fact that cataract is more prevalent to occur in female individuals (7). In the present study, it was shown that symptoms of the patients that were presented to the clinic with vision impairment, eye pain, eye redness, or high IOP had lasted averagely for 64.6 days. The study of Kothari et al. (6) has revealed that the duration of the onset PG symptoms in days was mostly 3 days or more than 14 days with two peaks, which are considerably less than the symptom duration of the patients in the present study. Furthermore, according to the results of the retrospective study that was conducted by Pradhan et al. (9), most of the patients had 10 days with onset symptoms of PG, which is again noticeably less than our results. Poor awareness of patients could be held accountable for the longer duration of the symptoms that was shown by the results of the present study.

Patients with PG occur to have severe visual impairments due to mature cataract formation and high IOP. In our study, it was seen that the patients had a mean BCVA of 0.10 decimals. In the study of Pradhan et al. (9), patients have had a preoperative BCVA of 0.32 decimals with subtly having better BCVA results, and, in another study conducted by Prajna et al. (8), patients were observed to have BCVA of 0.10 decimals which is the same result as the present study. As the cataract matures and surgery is delayed, IOP increases by narrowing the anterior chamber angle and causes difficulties in surgical procedures. The frequency of corneal edema increases depending on phacoemulsification power. The rates of inflammation seen in the eyes after ingestion of ripe cataracts are also higher (1). In our study, patients had a worsened BCVA at discharge from surgery (first-day examination) due to the inflammation, but on the contrary postoperative BCVA results happened to have a statistically significant increase. Various studies also showed that postoperative states of BCVA have been considerably better than the presented BCVA results (8-12).

Enlargement of the lens gives a push to the iris, resulting in the narrowing of the border between pupil margin and anterior capsule. Additionally, acute precipitations of the intumescent cataractous lens also cause angle narrowing. These two incidents lead to high IOP levels which are also called phacomorphic angle-closure or lens-induced glaucoma (1, 2). In the present study, it was revealed that the patients had a mean preoperative IOP of 32.3 mmHg. Many studies revealed similar results as the results of the present study (9, 11, 12). The first choice of treatment for high IOP in PG should be with medication, even though surgical removal of the lens is the definitive treatment. The response of PG to the treatment with medication is positive which results in lower IOP. The first approach to PG with medication treatment provides patients to have stable postoperative IOP without any need for further anti-glaucomatous medications when near normal to a normal level of IOP is achieved. According to our results, postoperative IOP has been observed to drop to the normal range, having an IOP lower than 21 mmHg, which was coherent to many other studies (8-12).

Phacomorphic glaucoma should be initially treated with medicinal approaches for a specific period before surgical procedures for a better outcome and sustained postoperative IOP. Nevertheless, the definitive treatment for PG is lens extraction surgery (5). In the present study, patients underwent intracapsular cataract extraction (ICCE) and phacoemulsification cataract extraction. As the results have shown, lens extraction has an important and positive impact on the prognosis of BCVA and IOP. The study of Moraru et al. (5) also pointed out the importance of lens extraction surgery in the prognosis of PG. Corneal edema and anterior chamber inflammation with a fibrous reaction on the first few days are the complications that specialists frequently come across in the early postoperative period. In the present study, corneal edema was observed on 47.4% of the patients but successfully treated with topical agents. Corneal edema was also shown to frequently occur in the early postoperative period by the study of Moraru et al. (5).

The main three limitations of the present study are the small number participating patients with PG, lack of data of premedication phase IOP due to being a tertiary ophthalmology clinic, and application of different types of lens extraction techniques such as phacoemulsification and ICCE. Missing surgical data of patients who underwent ICCE surgery on whether scleral fixation or anterior vitrectomy is received is another limitation to the present study and it is due to the application of old case files of participating patients. Procedures such as scleral fixation and anterior vitrectomy could also notably affect the outcomes of the patients who underwent these procedures. In addition, it is worth mentioning that being a tertiary ophthalmology clinic, patients come to us with referrals from other departments and are already treated with anti-glaucomatous agents. Thus, it challenges us to get the data of intraocular pressures of patients before medical treatment. Not all patients could be subjected to phacoemulsification due to challenging difficulties leading the specialists to proceed with ICCE or extracapsular cataract extraction. In our study, a certain number of patients were operated with the ICCE technique, which impacts the resulting BCVA due to bigger corneal incisions.

In conclusion, PG is angle-closure glaucoma that occurs in the basement of delayed lens extraction surgery and a mature cataract or intumescent cataractous lens. Therefore, individuals with a lens that has an increased density should undergo lens extraction surgery before significant complications occur. Lens removal through phacoemulsification or ICCE is an effective and safe procedure in the treatment of PG, ensuring satisfactory long-term IOP control and a rapid functional recovery. However, the rate of postoperative complications and the outcomes are better in patients treated with phacoemulsification. Nevertheless, not every case could be indicated to this type of surgical technique due to inoperative difficulties associated with the angle-closure. However, most of the patients are expected to have an outcome of favorable BCVA after surgery in the long term. Further studies are needed to thoroughly reveal the relationship between the treatment regimens and the progression and prognosis of the disease.

Ethics Committee Approval: This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2021/115).
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EVALUATION OF DEMOGRAPHIC, CLINIC AND GENETIC CHARACTERISTICS OF PATIENTS ADMITTED TO TRAKYA UNIVERSITY HOSPITAL WITH HYPERTROPHIC CARDIOMYOPATHY

Burak Bardakçı[1], Berfin Tan[1], Sarper Kızılkaya[1], Ceren Yüksel[1], Servet Altay[2]

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

ABSTRACT

Aims: This study aims to evaluate the genetics, clinical characteristics, and functional abnormalities of patients diagnosed with hypertrophic cardiomyopathy in Trakya University Hospital. ***Methods:*** This retrospective study was conducted with patients who were diagnosed with hypertrophic cardiomyopathy between November 2009 - November 2019 in Trakya University Hospital. The data were obtained from the hospital's database. Patients' data (regarding age, gender, genetics, transthoracic echocardiogram findings, medications, types of hypertrophic cardiomyopathy, and first diagnoses) were examined. Numbers, percentages, means, and standard deviations were used as descriptive statistics. ***Results:*** Eleven patients with hypertrophic cardiomyopathy were evaluated. Five (45.45%) were female and 6 (54.54%) were male. The mean age of the female patients was 58.20 ± 8.57 years. The most common type of hypertrophic cardiomyopathy was found to be asymmetrical septal cardiomyopathy [7 (63.63%)]. Three (27.27%) patients presented with hypertension. There were gene mutations in three patients. Among these three patients, two (18.18%) patients have MYBPC3, and one (9.09%) patient has TTN gene mutations. ***Conclusion:*** Hypertrophic cardiomyopathy is usually accompanied by comorbidities such as arrhythmias, myocardial infarction, coronary artery disease. Therefore, these patients must be paid attention to in these matters. ***Keywords:*** Hypertrophic cardiomyopathy, hypertension, sudden cardiac death

INTRODUCTION

Defined as the most inheritable group of cardiovascular diseases, cardiomyopathies differ in three major types based on the world's overall population prevalence: hypertrophic (1:500), dilated (1:2500), arrhythmogenic (1:5000) (1). With cases reported from more than 50 countries and having a ratio of 1:500 in the population, hypertrophic cardiomyopathy (HCM) is the most frequent of these three major types (2). Although many patients show either no or minor symptoms and are diagnosed incidentally, they may also display diverse symptoms such as exertional dyspnea, fatigue, unexplained syncope, atypical chest pain, arrhythmia, and sudden cardiac death (SCD) (1, 3, 4).

The diagnosis is primarily based on echocardiographic imaging of asymmetrical left ventricular hypertrophy without any symptoms of other cardiac or systemic diseases, but the assessments of left ventricular outflow tract gradients, systolic and diastolic function, and myocardial anatomy and function are also used for the diagnosis of HCM (5). Even though any segment of the myocardium can be affected due to HCM, almost 90% of the cases manifest that the septum is involved (6). According to the European Society of Cardiology guidelines, the diagnostic criteria for HCM is a left ventricular wall thickness of ≥15 mm measured with an echocardiogram or other imaging techniques (7).

Pivoting on different variables such as the reporting era or the source, the annual mortality risk of HCM spans from <1% in the general population to 3-6% in tertiary referral centers (8, 9). The reasons for HCM related deaths are varying, but according to the reports, heart failure, stroke, and SCD are the most occurring modes of death (8).

This study aims to examine clinical and genetic characteristics, cardiac structure and functional abnormalities of patients diagnosed with HCM in Trakya University School of Medicine, to assess HCM Risk-SCD score, and to establish if these factors affect the prognosis in the light of literature.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2020/440). In this retrospective study, patients who applied to Trakya University School of Medicine, Department of Cardiology and were diagnosed with HCM between November 2009 - November 2019 in Trakya University Hospital were evaluated respectively by their data. The data were obtained from the hospital database. Patients' data were examined regarding age, gender, family history, syncope history, arrhythmia history, septum thickness, apical thickness, ejection fraction, presence of pulmonary hypertension, presence of systolic anterior motion, history of mitral valve disease, presence of left atrial enlargement, genetic results, presence of a pacemaker, and 10-year mortality. Patients older than 18 years were included in the study.

Address for Correspondence: Burak Bardakçı, Trakya University School of Medicine, Edirne, TURKEY
e-mail: burakbardakci99@gmail.com
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Available at https://tmsj.trakya.edu.tr

ORCID iDs of the authors: BB: 0000-0002-0541-6991; BT: 0000-0002-9256-7631; SK: 0000-0002-7868-1585; CY: 0000-0003-2456-7282; SA: 0000-0001-7112-3970.

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The data were analyzed using IBM SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Numbers, percentages, mean, and standard deviation (SD) were used as descriptive statistics.

RESULTS

A total of 11 patients with various types of HCM were analyzed. Five (45.45%) of them were female and 6 (54.54%) of them were male. The mean age of the female patients was 58.20 ± 8.57 years and the mean age of the male patients was 46.67 ± 6.54 years. Four (36.36%) patients presented with chest pain, 3 (27.27%) patients presented with dyspnea, 3 (27.27%) patients presented with palpitation, and 1 (9.09%) patient was asymptomatic. Five of the patients were diagnosed with positive troponin and false axis at first. All the first diagnoses are shown in Table 1.

In our study group, the most common type of HCM was found to be asymmetrical septal cardiomyopathy [7 (63.63%)], followed by apical and midventricular types, respectively [3 (27.27%), 1 (9.09%)]. HCM types of patients and the distribution regarding gender are shown in Table 2.

Beta-blockers were the most frequently used medications, used by all patients in our study group [11 (100%)], followed by angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (ACEI/ARBs) [7 (63.63%)]. The distribution of the medications used by patients is shown in Table 3.

In our study group, arrhythmias [5 (45.45%)] were found to be the most common comorbidities, followed by coronary artery diseases [4 (36.36%)]. Atrial fibrillation (AF) and ventricular extrasystole were the most frequent types of arrhythmias with 3 (27.27%) patients affected. All fifteen comorbidities seen in our patient group are shown in Table 4.

Three (60%) female and 6 (100%) male patients presented with ischemic findings in the electrocardiogram. Five (45.45%) of the patients had left ventricle out track obstruction (LVOTO). Transthoracic echocardiogram (TTE) showed systolic anterior movement in three (27.27%) patients. TTE findings are shown in Table 5.

Data regarding genetic mutations were available only for 5 patients. Among these five patients, two (18.18%) patients have MYBPC3 and one (9.09%) patient has TTN gene mutations.

Table 1: First diagnoses of the patients.

First Diagnosis	*Number (%)*
Screening due to family history	1 (9.09)
Elevated troponin level and false axis	5 (45.45)
Clinical consult due to symptoms	3 (27.27)
ECG/TTE findings and hypertension	2 (18.18)

ECG/TTE: *Electrocardiogram/transthoracic echocardiogram*

Table 2: Hypertrophic cardiomyopathy types of the patients.

HCM Type	*Total [n (%)]*
Asymmetrical septal	7 (63.64)
Apical	3 (27.27)
Midventricular	1 (9.09)

HCM: *Hypertrophic cardiomyopathy*

Table 3: Medications used by the patients.

Medication	*Number (%)*
ACEI/ARBs	7 (63.63)
Calcium channel blockers	2 (18.18)
Beta blockers	11 (100)
Oral anticoagulants	2 (18.18)
Diuretics	5 (45.45)
Acetylsalicylic acid	6 (54.54)
Amiodarone	2 (18.18)
Statins	4 (36.36)
Antidiabetics	1 (9.09)

ACEI/ARBs: *Angiotensin converting enzyme inhibitor/angiotensin receptor blockers*

Table 4: Comorbidities of the patients.

Comorbidity	*Number (%)*
Hypertension	3 (27.27)
Diabetes mellitus	2 (18.18)
Coronary artery disease	4 (36.36)
Chronic kidney disease	3 (27.27)
Myocardial infarction	2 (18.18)
Cerebrovascular accident	1 (9.09)
Cardiac abnormality	1 (9.09)
Atrial fibrillation	3 (27.27)
Ventricular tachycardia	1 (9.09)
Any type of arrhythmia	5 (45.45)
Chronic liver disease	1 (9.09)
VEA in Holter	3 (27.27)
Cardiac arrest	1 (9.09)
Death	1 (9.09)
Complications of HCM	3 (27.27)

VEA: *Ventricular extrasystole,* ***HCM:*** *Hypertrophic cardiomyopathy*

Table 5: Transthoracic echocardiogram findings' distribution regarding patients' gender.

TTE Findings	*Female (mean ± SD)*	*Male (mean ± SD)*
LV diastolic diameter (mm)	44 ± 1.67	45.67 ± 0.84
Diastolic IVS thickness (mm)	16 ± 2.34	17 ± 2.66
EF (%)	59 ± 1.87	60.17 ± 1.86
LA diameter (mm)	36.80 ± 3.45	42.5 ± 1.17
LV systolic diameter (mm)	26.20 ± 1.06	24.67 ± 1.49
Diastolic posterior wall thickness (mm)	11.60 ± 1.02	13.33 ± 1.83
Ascending aorta diameter (mm)	34.40 ± 3.32	31 ± 0.73
Aortic root (mm)	21.5 ± 1.50	20.33 ± 1.45

TTE: *Transthoracic echocardiogram,* ***SD:*** *Standard deviation,* ***LV:*** *Left ventricle,* ***IVS:*** *Interventricular septum,* ***EF:*** *Ejection fraction,* ***LA:*** *Left atrium*

DISCUSSION

The mean age of our study was 58.20 ± 8.57 years for female and 46.67 ± 6.54 years for male patients, which was in line with literature (10, 11).

While the studies conducted by van Velzen et al. (10) and Olivotto et al. (11) showed comparable results on the frequencies of symptoms between these studies, [these results being 18% of patients presenting with chest pain, 14% presenting with dyspnea, and 8% presenting with palpitations on the study of van Velzen et al. (10) and 12%, 14%, and 8%, respectively in the study of Olivotto et al. (11)], our study showed patients more frequently presenting with symptoms, 36.36% with chest pain, 27.27% with dyspnea, and 27.27% with palpation. It should be noted that both studies included a higher number of patients than our study.

In general, the most common type of hypertrophy is asymmetrical hypertrophy, and it is followed by left ventricular hypertrophy (2). Also, in our study, we found the most common type of hypertrophy as asymmetrical hypertrophy, but in contrast, there were no patients with left ventricular hypertrophy. This may be due to the small number of patients.

Beta-blockers and ACEI/ARBs are the most commonly used medications among our patients. Beta-blockers are the first-line medications of treatment of the HCM (4). ACEI/ARBs are used in many conditions which may accompany such as hypertension, coronary artery disease, chronic kidney disease, or diabetes mellitus (12, 13). All these accompanying conditions are common among our patients.

Although it remains ambiguous whether there is a positive association between HTN and HCM, literature shows statistically significant differences between HCM with or without accompanying HTN (14, 15).

Another evaluation was done based on gene mutations. Although gene mutations are thought to be the founding cause of HCM, in our study, only three patients out of 11 were observed to have causative mutations (16). Two (18.18%) had MYBPC3 gene mutations and one (9.09%) had TTN gene mutations. Contrary, in a study by Richard et al. (17), 43% of the patients showed MYBPC3 gene mutations. Another study also showed MYBPC3 mutations in 39% of patients (10). Our limited number of patients may cause different results with the literature.

One of HCM's main defining features and one of the biggest factors on its prognosis is LVOTO (18). In our study, LVOTO was observed in 45.45% of the patients. Maron et al. (19) saw the same factor in 25% of the patients in their study.

Two (18.18%) of our patients had a history of myocardial infarction (MI). MI may occur due to myocardial bridging, coronary circulatory insufficiency due to hypertrophy, or high diastolic pressure (20, 21). Since serum levels of troponin are elevated in both MI and HCM, these two patients may be misdiagnosed with MI. Also, it may cause the diagnosis of MI to be overlooked.

Atrial fibrillation represents the most common sustained arrhythmia in both general and HCM populations (22). With the reported prevalence of 18-28%, AF appears to be 4 to 6 times more common in patients with HCM (22). In our study, AF was the most common type of arrhythmia with a 27.27% ratio, in line with the literature.

Sudden cardiac death is the most frequent cause of sudden death among athletes and the most common cause of SCD is HCM among this population (20). There were one ventricular tachycardia and one SCD case in our study. Therefore, HCM patients should be followed up for SCD. Implantable cardioverter-defibrillators should be placed in patients with high HCM risk-SCD score.

The small number of subjects is the main limitation of our study. Moreover, it is a retrospective, single-center study. A multi-center study or a more extensive period of time could have wielded results closer to those of current literature and could have been more illuminating on various connections of different factors of HCM. Further research could include more detailed data on family histories and genetic markers of HCM.

In conclusion, this study provided general information on the clinical and genetic characteristics of HCM. Further studies are needed to overcome the limitations and enlighten more of the nature of HCM, its accompanying factors, and their effects on the diagnosis.

Ethics Committee Approval: This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2020/440).
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BILATERAL ELECTROCONVULSIVE THERAPY FOR POST-TRAUMATIC STRESS DISORDER COMORBID TO DEPRESSION

Erhan Kavakbasi[1], Goktug Mert Ciftci[1], Bernhard T. Baune[1, 2]

[1]Department of Psychiatry, University Hospital Münster, Münster, GERMANY
[2]Department of Psychiatry, Melbourne Medical School, University of Melbourne, Melbourne, AUSTRALIA

ABSTRACT

Aims: We aim to present a patient who was suffering from treatment-resistant depression along with psychotic features and comorbid post-traumatic stress disorder and was treated by bilateral electroconvulsive therapy. ***Case Report:*** A 58-year-old female patient was transferred to the University Hospital Münster with the diagnosis of treatment-refractory depression with psychotic features and post-traumatic stress disorder. The patient was non-responsive to unilateral electroconvulsive therapy and multiple antidepressant agents during several inpatient treatments. After initiating bilateral electroconvulsive therapy, the patient's symptoms improved significantly. ***Conclusion:*** After ruling out conventional treatment algorithms for psychotic depression comorbid to post-traumatic stress disorder, physicians can consider bilateral electroconvulsive therapy to treat complicated cases. ***Keywords:*** Stress disorders, post-traumatic, electroconvulsive therapy, depressive disorder, psychotic disorders

INTRODUCTION

Treatment-resistant depression with auditory hallucinations and comorbid post-traumatic stress disorder (PTSD) is a diagnostic and therapeutic challenge in which the role of electroconvulsive therapy (ECT) is unclear (1). A systematic review concluded that, because of the small number of cases, it remains unclear if favorable outcomes are conditioned by the improvement of depression symptoms without beneficial effects on core PTSD symptoms (1). We report the case of a 58-year-old female patient with treatment-refractory depression and PTSD, who responded neither to unilateral ECT nor to multiple antidepressant agents during several inpatient treatments. However, she achieved remission after bilateral ECT.

CASE REPORT

The present episode of depression began two years ago and was accompanied by psychotic features. The key symptoms were severely depressed mood, anhedonia, psychomotor agitation, suicidal ideations, and concentration difficulties. The patient heard the suicide-commanding and insulting voices of her father, who had abused her during her childhood. This put her under so much pressure that she only trembled and could no longer hold an orderly conversation. In addition, she suffered from flashbacks and intrusions.

Before her admission to our hospital, it had not been possible to distinguish the patients' condition between depression with psychotic symptoms and PTSD with psychosis-related experience, because the voices referred almost exclusively to previous traumatic events. She had been hospitalized for psychiatric treatment multiple times for several months during the same episode without achieving remission. Therefore, she was transferred to our university hospital. Due to treatment resistance, we started a series of bitemporal ECT. Before ECT, the patient showed a high score in Beck's Depression Inventory-II (BDI-II: 52) and had severe PTSD symptoms, showing a score of 7 in Clinical Global Impressions – Severity Scale. The patient showed a rapid response with clinical improvements after the second ECT session. After the 7th ECT, a remission of the depressive episode was recorded (BDI-II: 8). Symptoms of PTSD had also significantly improved, having a score of 1 on the Clinical Global Impressions – Improvement Scale. The auditory hallucinations, as well as flashbacks and intrusions, disappeared completely. As a side effect of ECT, dizziness and slight memory deficits occurred, but these only lasted for a few hours. Maintenance ECT sessions at ever-increasing intervals were planned.

DISCUSSION

With major depression, comorbid PTSD, and auditory hallucinations, ECT may be an adequate therapeutic approach. Bilateral ECT was shown to be as similarly effective as high dose right unilateral ECT with acute depression, whereas low-to-moderate dose right unilateral ECT was found to be non-superior to sham treatment (2). Our case shows that ECT should not be considered ineffective before the bitemporal stimulation technique is used. Patients who have not responded to unilateral stimulation may still respond very well to bitemporal stimulation.

Acoustic hallucinations related to past maltreatment can be difficult to classify when there is PTSD comorbid to severe depression. Only a few studies show the effectiveness of ECT in improving the symptoms and reducing the suicide rate in patients with severe depression and comorbid PTSD (3, 4). Our case shows that ECT should be considered as a therapeutic option in these patients and can be very effective, even after no response to unilateral stimula-

Address for Correspondence: Goktug Mert Ciftci, Department of Psychiatry, University Hospital Münster, Münster, GERMANY
e-mail: ciftcig@uni-muenster.de
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ORCID iDs of the authors: EK: 0000-0002-4261-7450; GMC: 0000-0003-2364-6317; BTB: 0000-0001-6548-426X.

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tion. Our patient had no memory loss regarding the maltreatment in her childhood, which was discussed as the mechanism of action of ECT in these patients (5). Prospective, randomized, and controlled trials are needed to determine the effectiveness of ECT in these patients.

Technical Parameters of ECT Device

ECT was performed with THYMATRON® SYSTEM IV. Thiopental was used as an anesthetic agent for ECT. An age-based dosing method was used.

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HYDATID CYST IN A HEART FAILURE PATIENT MIMICKING PHANTOM TUMOR

Irmak İrem Özyiğit[1], Beliz Koçyiğit[1], Servet Altay[2]

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

ABSTRACT

Aims: We aimed to present a heart failure patient with a hydatid cyst of the lung, mimicking a phantom tumor. ***Case Report:*** A 71-year-old male patient presented to the cardiology department of Trakya University School of Medicine with increasing shortness of breath and cough. His hospital admission complaints, heart failure history, and chest radiology results were consistent with a phantom tumor of the lung secondary to congestive heart failure. The patient was given diuretics; however, there was no evidence of resolution or change in the size of the observed cystic lesion. A hydatid cyst as a differential diagnosis was considered, and subsequent questioning of the patient revealed animal contacts. The patient was offered the option of surgical removal of the cyst, which he declined due to the high mortality risk. The patient was prescribed 400 mg of albendazole and was advised to have regular check-ups. In the long term, he showed no further signs and symptoms of hydatid cyst. The hydatid cyst was neither removed nor disappeared, and it continued to be visible on radiological follow-up examinations. ***Conclusion:*** Due to the similarities present in admission complaints and chest examinations, it is challenging to differentiate hydatid cyst of the lung in heart failure patients. Physicians should be aware of the hydatid cyst in the differential diagnosis of pleural cysts and consider patients' occupation and residency in order to not overlook zoonotic diseases. ***Keywords:*** Hydatid cyst, phantom tumor, congestive heart failure

INTRODUCTION

Human echinococcosis is a zoonosis caused by tapeworms of the genus Echinococcus (1). *Echinococcus granulosus* is responsible for cystic echinococcosis, also known as hydatidosis or hydatid disease (1, 2). Its definitive hosts are dogs and other carnivores such as red foxes, coyotes, and dingos (2). Its intermediate hosts are mainly sheep, cattle, goats, and pigs (2). The parasite is transmitted to definitive hosts when they consume the internal organs of intermediate hosts that contain the hydatid cysts (1, 2). Humans can be accidental hosts when the parasite is transmitted to them through the consumption of soil, water, or food that has come into contact with the feces of a definitive host (3).

Infestation with *Echinococcus granulosus* results in the formation of one or more hydatid cysts located primarily in the liver and lungs (2). The incubation period can last from a few months to many years (1). Most cases remain asymptomatic until the hydatid cysts become large enough for the patient to present with clinical symptoms (4). Clinical manifestations depend on the location of the cyst and may vary depending on its size (1). The most common symptoms of pulmonary cystic echinococcosis are cough, chest pain, dyspnea, and hemoptysis (5). Diagnosis of cystic echinococcosis is primarily by ultrasonography, supplemented by computed tomography and magnetic resonance imaging (4). Cysts may also be detected incidentally by imaging studies such as radiographs performed for other indications (4). In small, uncomplicated pulmonary cysts, benzimidazoles showed good efficacy when used alone (6). Preoperative administration of benzimidazoles should be avoided for larger lung cysts (6). Surgical interventions aimed at eliminating the parasite and treating the related pathology should be as conservative as possible (6). However, radical surgery may be required in cases of extensive parenchymal involvement, severe pulmonary suppuration, and complications (6).

When it comes to the differential diagnosis of hydatid cysts on chest X-ray, they can mimic various lung pathologies such as metastases, carcinoma, fluid-filled cysts, and inflammatory masses (7). In our case, the differential diagnosis was made with a phantom tumor. A phantom tumor is defined as an accumulation of fluid in the interlobar spaces of the lung, radiologically simulating a neoplasm, and usually secondary to congestive heart failure (8, 9). In this case report, we aim to present the diagnosis of a hydatid cyst mimicking a phantom tumor in a patient with heart failure.

CASE REPORT

A 71-year-old male patient was admitted to the cardiology department of Trakya University School of Medicine with increased shortness of breath and cough. He was an ex-smoker with a history of coronary artery disease (stents were implanted three years ago), hypertension, diabetes mellitus, myasthenia gravis, chronic obstructive pulmonary disease, congestive heart failure, ischemic cardiomyopathy, and atrial fibrillation. In the last three years, he frequently visited the emergency room with complaints of heart failure. A year ago, he was hospitalized for cardiopulmonary arrest where he received an implantable cardioverter-defibrillator for secondary protection. To treat his congestive heart failure and

Address for Correspondence: Irmak İrem Özyiğit, Trakya University School of Medicine, Edirne, TURKEY
e-mail: iiozyigit@gmail.com
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ORCID iDs of the authors: IİÖ: 0000-0003-2443-0155; BK: 0000-0001-6056-0219; SA: 0000-0001-7112-3970.

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hypertension, he was treated with diuretics. He was also taking 2.5 mg of ramipril, sacubitril/valsartan, 15 mg of rivaroxaban, 20 mg of isosorbide dinitrate, 20 mg of furosemide, and eplerenone.

The patient was admitted to the cardiology department for shortness of breath associated with his known congestive heart failure. The patient's X-ray revealed a cystic lesion in the lower side of the right lung (Figure 1). There was no evidence of a cystic lesion on the chest X-ray performed two months ago. Based on the history and radiological findings, he was diagnosed with a phantom tumor of the lung secondary to congestive heart failure. The patient received intensive diuretic treatment.

At follow-up, the physicians requested a contrast-enhanced computed tomography scan, which showed a cystic nodule with a smooth contour and a diameter of approximately 4 cm in the middle-lower lobes of the right lung (Figure 2). There was no evidence of resolution or change in the size of the observed cystic lesion. Although the location of the lesion and the history of heart failure suggested a diagnosis of phantom tumor, the lack of response to diuretic treatment ruled out this initial diagnosis. The patient was then consulted by the department of thoracic surgery who evaluated his radiological findings and medical history. They considered a hydatid cyst as a differential diagnosis, and subsequent questioning of the patient revealed that animal contacts and village housing supported this new diagnosis.

Following the diagnosis of a hydatid cyst, the patient was offered the option of surgical removal of the cyst, which he declined due to the high risk of the procedure. Subsequently, the patient was prescribed 400 mg of albendazole and was advised to have regular check-ups. In the long term, he showed no further signs and symptoms of hydatid cyst. The hydatid cyst was neither removed nor disappeared, and it continued to be visible on radiological follow-up examinations (Figure 3). His hospitalizations related to heart failure continued, and the patient died in the cardiology department one year after the diagnosis of his hydatid cyst.

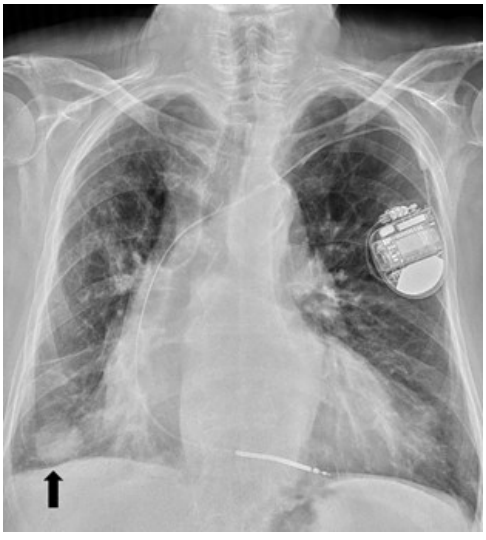

Figure 1: Posteroanterior chest radiography revealing hydatid cyst (Arrow).

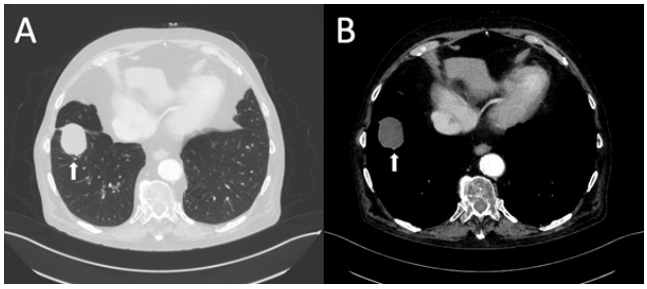

Figure 2: The computed tomography images reveal a hydatid cyst (Arrows). A: Lung parenchyma window. B: Mediastinal window.

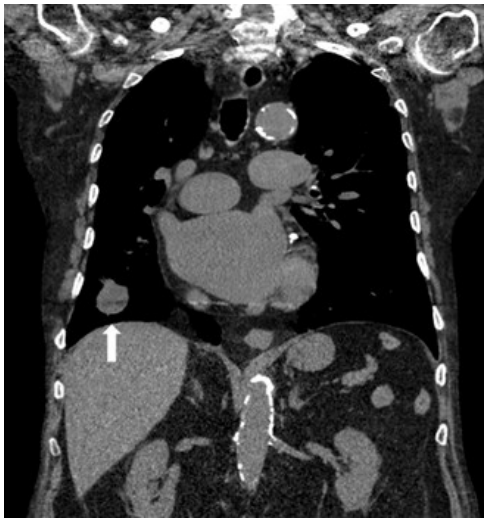

Figure 3: Coronal plane imaging of the patient. The computed tomography scan of the thorax shows a hydatid cyst (Arrow).

DISCUSSION

Hydatid cyst is the result of zoonotic infestation by tapeworms (1). The two main species of these tapeworms found in the alveolar system are *Echinococcus granulosus* and *Echinococcus multilocularis* (6). In our case, we are concerned with *Echinococcus granulosus* because this tapeworm is responsible for cystic echinococcosis, which we refer to as a "hydatid cyst" because of the disease it causes (1, 6). Accidental hosts, in this case humans, can get these parasites through contaminated products such as food or water that have come into contact with feces (3).

Patients with congestive heart failure tend to develop phantom tumors, and the right hemithorax is the most common area in the lung where they occur (10). Our patient's X-ray revealed a cystic mass on the lower side of the right lung, and he had a known history of heart failure. A presumptive diagnosis of a phantom tumor secondary to congestive heart failure was made. The rapid development of this mass supported this initial diagnosis. In patients with heart failure, it is advisable to think of a phantom tumor when a cystic mass appears on the X-ray to avoid unnecessary interventions and treatments (11).

The admission complaints of phantom tumors may include dyspnea and dry cough, which are very similar to symptoms of a hydatid cyst. Frequently encountered complaints include chest pain, cough, dyspnea, and hemoptysis in pulmonary cystic echinococcosis (5, 12). In our case, the patient presented with shortness of

breath and cough, which in conjunction with his history was reminiscent of a phantom tumor. Similarly, in the case of Canpolat et al. (13), a patient presented with dyspnea and cough.

Phantom tumors are treatable with diuretics and a reduction in fluid intake (14). If the treatment plan is followed, complete regression of the tumor can be expected. In this case, the patient was treated with diuretics based on his initial diagnosis. Although the history of heart failure and location of the mass were relevant to phantom tumors, no regression or change in size was observed. Failure to respond to treatment was the main reason physicians considered other diagnoses. The final diagnosis was made based on chest X-rays and a history of animal contact. As a result, hydatid cyst was chosen as a differential diagnosis, which is endemic in our country (15). Demirci et al. (15) collected cases of hydatid cysts in a Turkish city and found that the lung was the second most common location. Definitive treatment of a hydatid cyst requires removal of the cyst by open surgery (16). In addition, albendazole can be added to the treatment plan preoperatively and/or postoperatively to prevent recurrence and achieve complete healing (16).

Complete healing was possible with surgical intervention and could prevent the compression caused by the mass, but our patient refused surgical removal of the cyst due to the high risk of mortality (13, 16). For this reason, only drug treatment, albendazole 400 mg, was initiated. In the long term, the hydatid cyst was neither removed nor disappeared, and it was still visible on radiological follow-up examinations. Although the main drug treatment for hydatid cysts in the lungs, heart, and liver was albendazole, the study by Dehkordi et al. (16) showed that albendazole had no effect on cysts in the lungs.

The diagnosis of a hydatid cyst can be difficult in patients with heart failure because of the similarities between the symptoms on admission and chest X-rays. Physicians should think of hydatid cyst in the differential diagnosis of pleural lesions. Also, we recommend physicians consider the occupation and residence of their patients, especially to remind them of zoonotic diseases.

Ethics Committee Approval: N/A

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

Conflict of Interest: The authors declare no conflict of interest.

Author Contributions: Concept: İİÖ, BK, SA. Design: İİÖ, BK, SA. Supervision: İİÖ, BK, SA. Resources: İİÖ, BK, SA. Materials: İİÖ, BK, SA. Data collection and/or Processing: İİÖ, BK, SA. Analysis and/or Interpretation: İİÖ, BK, SA. Literature Search: İİÖ, BK, SA. Writing Manuscript: İİÖ, BK, SA. Critical Review: İİÖ, BK, SA.

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SUCCESSFUL MANAGEMENT OF PERIPARTUM CARDIOMYOPATHY IN A YOUNG FEMALE PATIENT

Ceren Yüksel[1], Bengisu Çıray[1], Mustafa Alperen Koşucu[1], Servet Altay[2]

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

ABSTRACT

Aims: Peripartum cardiomyopathy is a rarely seen pregnancy-related myocardial disorder. The diagnosis is usually challenging and is made by exclusion. We aimed to present the recovery of a patient with peripartum cardiomyopathy as a result of a successful treatment plan. ***Case Report:*** A 26-year-old female patient with type-2 diabetes mellitus presented to the cardiology department of Trakya University School of Medicine. The patient experienced dyspnea and edema after delivery at 37 weeks of gestation. After the results of the blood tests, further cardiac examinations were deemed necessary. The echocardiogram revealed a low ejection fraction, indicating heart failure. The patient was recommended to halt breastfeeding and bromocriptine treatment was started. The patient was discharged one week later and kept under follow-up. ***Conclusion:*** Peripartum cardiomyopathy is a rare disease and therefore not easy to diagnose, but with appropriate treatment plans and frequent follow-ups, patients have high chances of full recovery. ***Keywords:*** Peripartum, cardiomyopathy, pregnancy, bromocriptine, heart failure

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a type of heart failure that mostly affects previously healthy women in the puerperium, presenting with symptoms indicating congestion such as pulmonary rales, peripheral edema, and jugular vein distention (1). PPCM is characterized as left ventricular systolic dysfunction (LVSD) and ejection fraction (EF) below 45%, which means that the blood pumped to the body is decreased and not sufficient (2). PPCM may heal on its own, but it can cause serious complications as it occurs with rapid clinical worsening. Garg et al. (3) state that although the underlying cause of the disease is not fully understood, multiparity, pregnancy over 30 years of age, race, twin pregnancy, obesity, hypertension, and eclampsia are among the risk factors. Apoptosis, the effect of prolactin hormone, endothelial mechanism disorders, autoimmune reactions, and inflammation are other reasons suggested for the development of this disease (4).

Peripartum cardiomyopathy is a rare clinical condition (1). As reported by Abboud et al. (5), according to individual studies that have been conducted, the incidence varies, with estimates ranging from 1 in 1,300 to 1 in 15,000. Additionally, Garg et al. (3) state that the prevalence is increased in people of African descent; the incidences estimated by studies are 1 in 1000 live births in South Africa, about 1 in 2289-4000 live births in the United States, and 1 in 299 live births in Haiti. Early diagnosis is difficult with LVSD and EF below 45%, as symptoms are indeed common in almost all women after pregnancy (5). Although early diagnosis is difficult, it is a key factor in the prognosis of the disease, which could be life-saving for the patient (6).

We present the case of a patient with PPCM with a history of diabetes mellitus. As PPCM is a rare condition diagnosed by exclusion, we hope to contribute to the literature and raise awareness about PPCM.

CASE REPORT

A 26-year-old female patient with a history of type-2 diabetes mellitus presented to the cardiology department of Trakya University School of Medicine due to increased dyspnea and edema after delivery at 37 weeks of pregnancy. The patient was diagnosed with preeclampsia and edema at 34 weeks gestation. The patient was admitted to the cardiology service due to increased dyspnea. According to the patient's hemogram, her hemoglobin was 10.9 g/dl, her hematocrit value was 33.2%, and her NT-ProBNP was 4753 pg/ml, which is significantly higher than the normal range (0-125 pg/ml), indicating heart failure. In the echocardiogram, the patient had an EF of 34%. Global left ventricular hypokinesia, LVSD, left ventricular diastolic dysfunction, and left ventricle dilatation were observed. In addition to these findings, mild aortic insufficiency, mild tricuspid regurgitation, and moderate mitral regurgitation were detected. Because of the patient's history of diabetes, a selective coronary angiography was performed, and the angiogram showed no abnormalities. An endocrinology consultation was requested for the patient's treatment plan. After the consultation, bromocriptine treatment was started and breastfeeding was halted. In addition to bromocriptine, which is a dopamine receptor agonist, treatment for heart failure was started. Beta-blockers, diuretics, and angiotensin-converting enzyme inhibitors were used for the treatment

Address for Correspondence: Ceren Yüksel, Trakya University School of Medicine, Edirne, TURKEY
e-mail: crnyuksel2@gmail.com
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ORCID iDs of the authors: CY: 0000-0003-2456-7282; BÇ: 0000-0001-6332-7543; MAK: 0000-0002-2381-5099; SA: 0000-0001-7112-3970.

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of heart failure. After the consultation, endocrinology, nephrology, and cardiology follow-ups were recommended and the patient was discharged. She was prescribed 6.25 mg of carvedilol, 25 mg of spironolactone, 5 mg of ramipril, 40 mg of pantoprazole, 5 mg of ivabradine, and insulin glulisine and insulin glargine.

Echocardiography and cardiac magnetic resonance imaging (MRI) were performed one month after discharge, and the patient had an EF of 45%. Cardiac MRI showed depressed left ventricle contraction (Figure 1), and it was decided to continue the treatment. In the third month of the treatment, the patient became pregnant unintentionally, and a medical abortion was performed since she had an EF of 45%. The patient was followed up in the sixth month and first year of her treatment. She had no complaints at her last follow-up and had an EF of 60%.

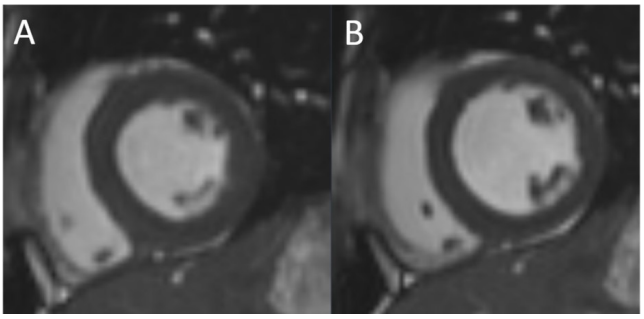

Figure 1: Cardiac MRI images in short axis steady-state free precession, depressed left ventricle contraction is observed. A: During systole. B: During diastole.

DISCUSSION

Diagnosing peripartum cardiomyopathy is difficult because its initial symptoms are common among pregnant and postpartum women. Moreover, PPCM presents without any previous heart-associated conditions and shows a rapid clinical worsening if not diagnosed on time and treated immediately. It is crucial to consult a cardiologist when a pregnant or postpartum patient applies to the hospital complaining of shortness of breath. After running diagnostic tests such as an echocardiogram, blood tests, and cardiac MRI, it should be evaluated whether the patient has PPCM, and a treatment plan should be established accordingly.

Besides the standard treatment for reduced EF, PPCM patients are also treated with a prolactin release inhibitor, bromocriptine (7). Bromocriptine usage on patients is rationalized by a hypothesis that claims that the heart of a postpartum woman would have increased oxidative stress levels. This oxidative stress would trigger the cathepsin D-mediated cleavage of prolactin into a 16-kDa subform, thus affecting angiostatic and proapoptotic properties, benefitting myocardial microvascular injury, and blocking endothelial cell proliferation and migration (7). Considering that one of the primary goals of using bromocriptine as a therapy option of PPCM is to suppress prolactin release, discontinuation of breastfeeding is significant since breastfeeding stimulates prolactin.

European Society of Cardiology proposes a treatment plan called "the BOARD scheme" which implies that the treatment of PPCM should include bromocriptine, oral heart failure therapies, anticoagulants, vasorelaxant agents, and diuretics (8). In our case, the patient's medication regimen included beta-blockers (carvedilol), diuretics (spironolactone), angiotensin-converting enzyme inhibitors (ramipril), and 2.5 mg of bromocriptine. Pantoprazole was prescribed for lowering the amount of acid released in the stomach. In order to slow her heart rate, the patient was prescribed ivabradine. Because our patient had type-2 diabetes mellitus, she continued using insulin glulisine and insulin glargine.

A review of case studies on the use of bromocriptine in peripartum cardiomyopathy patients conducted by Simon et al. (9) displays the recovery in low left ventricular EF when 2.5-5 mg of bromocriptine is used alongside standard heart failure therapy. Our patient's recovery process is also evidentiary to Simon et al. (9)'s review since her LVEF was first measured 30%, and after using 2.5 mg bromocriptine daily, the LVEF was measured as 60% at the 6th-month follow-up.

Peripartum cardiomyopathy treatment is highly effective as the patients have a 50% chance of recovery and 98% chance of survival (9). Mortality rates differ regionally. As reported from single-center studies from Brazil and Haiti, their mortality rates are reported to be 14-16% in a month's interval (3). Biteker (10) stated that in two different studies investigating PPCM in Turkey, the mortality rate differs from 25% to 30%.

Unfortunately, the recurrence rate of PPCM is high and patients are advised to seek counseling from a perinatologist in order to avoid future pregnancies (11). In our case, the patient got accidentally pregnant in the third month of the treatment process. Since the patient had an EF of approximately 45%, which is not sufficient for keeping the patient's condition stable, a medical abortion had to be performed and their pregnancy was terminated. In conclusion, PPCM can cause heart failure, and even death, if not diagnosed on time and treated immediately. Therefore, it is cruicial not to overlook the possibility of peripartum cardiomyopathy, especially in young patients presenting with dyspnea or edema.

Ethics Committee Approval: N/A
Informed Consent: Informed verbal consent was obtained from the patient for this study.
Conflict of Interest: The authors declare no conflict of interest.
Author Contributions: Concept: CY, BÇ, MAK, SA. Design: CY, BÇ, MAK, SA. Supervision: CY, BÇ, MAK, SA. Resources: CY, BÇ, MAK, SA. Materials: CY, BÇ, MAK, SA. Data collection and/or Processing: CY, BÇ, MAK, SA. Analysis and/or Interpretation: CY, BÇ, MAK, SA. Literature Search: CY, BÇ, MAK, SA. Writing Manuscript: CY, BÇ, MAK, SA. Critical Review: CY, BÇ, MAK, SA.
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RETRACTIONS & ERRATA

Date: 2021, October

Errata

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".

8th Volume Index
SUBJECT INDEX
February 2021 - October 2021

8th Volume Index
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Contribution	Explanation	Contributing Authors
CONCEPT	The idea for research or article/hypothesis generation.	
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SUPERVISION	Supervision and responsibility for the organization and course of the project and the manuscript preparation.	
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3. I understand that the case report will be published without my name attached and researchers will make every attempt to ensure my anonymity. I understand, however, that complete anonymity cannot be guaranteed.
4. I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Name of Participant: _____

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