

CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF TAKAYASHU'S ARTERITIS: PATIENT REPORT

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Takayashu's arteritis is a chronic, immune-mediated vasculitis of the large blood vessels, which usually occurs in patients younger than 50 years and primarily affects the aorta and its main branches. The majority of affected are women. A patient with Takayashu's arteritis who first visited the doctor due to fatigue, palpitations and rapid heart rate is presented. On clinical examination, over both carotid arteries, audible murmurs, the pulse of the right radial artery is very weak, and the pulse of the left radial artery is not palpable. Laboratory analyzes revealed increased sedimentation of erythrocytes and the level of C-reactive protein. The diagnosis of the disease was confirmed by Doppler ultrasound of blood vessels, computed tomography angiography (CTA) and positron emission tomography (18 F-FDG PET/CT). The patient fulfilled five out of six criteria for the clinical diagnosis of Takayashu's arteritis of the American College of Rheumatology and belonged, according to the angiographic and clinical classification of Takayashu's arteritis, to Type I. She was treated with corticosteroids, immunosuppressants and percutaneous transluminal angioplasty.

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Key words: *Takayashu's arteritis, Macaroni sign, Doppler of blood vessels, Multislice computed tomography, positron emission tomography / computed tomography*

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Introduction

Takayashu's arteritis is a chronic, immune-mediated vasculitis of the large blood vessels, which usually occurs in patients younger than 50 years and primarily affects the aorta and its main branches, the carotid, subclavian, renal, coronary, digestive, and iliac arteries (1). It is also known as pulseless disease, aortic arch syndrome, thromboaropathy and thromboarteriopathy.

The disease is widespread throughout the world but is thought to be much more common in Asian populations. The total annual incidence of Takayashu's arteritis is 0.3 to 3.4, and the

prevalence is 0.9 to 40 per million inhabitants. The majority of affected are women with a female-to-male ratio ranging from 5:1 to 9:1 in favor of women (1).

The etiology of Takayashu's arteritis has not been clearly defined so far, but it is believed that genetic predisposition, the autoimmune nature of the disease and environmental factors play an important role in its genesis (2).

Both humoral and cellular immune mechanisms are involved in the pathogenesis of Takayashu's arteritis. Constant activation of immune cells and continuous release of pro-inflammatory cytokines in the adventitia and arterial media leads to chronic vascular inflammation, thickening of the adventitia, intimo-medial hyperplasia due to cell infiltrates, fibrosis of the media and intima, which can lead to artery stenosis or occlusions, occasional thrombosis or aneurysm formation (3).

Pathohistological examination of the wall of the affected arteries shows medial-adventitial giant cell panarteritis. In the acute phase, inflammatory infiltrates in the adventitia predominate, which in the chronic phase are replaced by fibrous lesions and arterial calcifications (4).

It has been confirmed that the inflammatory infiltrates consist of CD4, CD8, gamma delta T lymphocytes, natural killer cells (NK cells), macrophages and neutrophils, as well as the production of Tumor necrosis factor-alpha (TNF-α), which is important in the formation of granulomas,

takes place primarily in macrophages, T cells and NK cells. Pathohistological findings of aortic tissue samples show that gamma delta T and NK cells are involved in endothelial cell apoptosis by producing perforin (5).

Clinically, Takayashu's arteritis is characterized by an acute phase with general symptoms, fever, higher temperature, night sweats, loss of appetite and body weight, fatigue and weakness, muscle and joint pain followed, months or years later, in a chronic phase with symptoms and signs caused by stenosis or occlusion of blood vessels, manifested by rapid fatigue, lack of effort, heart palpitations and rapid heartbeat, hard breathing and feeling of pressure in the chest, reduced or absent pulse, difference in blood pressure between the arms, dizziness, fainting, headache, increased blood pressure and visual impairment. In most patients, there is an overlap of both phases and their corresponding symptoms (3). The diagnosis of Takayashu's arteritis is based on a group of clinical, biological, radiological and sometimes histological elements (4).

In the diagnosis and follow-up of patients with Takayashu's arteritis, the most significant application is the use of Doppler echosonography of blood vessels, computed tomography with contrast angiography (CTA), nuclear magnetic resonance angiography (NMR) and positron emission tomography with the use of a radiolabel - fluorodeoxyglucose (18FDG PET-CT) (6).

The progression of Takayashu's arteritis is variable and about 50% of sufferers have recurrence or development of vascular complications within 10 years of the diagnosis of the disease (4).

In the therapy of Takayashu's arteritis, corticosteroids are used as the basic and most effective drugs, immunosuppressants in patients who have a disease with high activity and when the dose of corticosteroids should be reduced and biological drugs. (5). In symptomatic stenotic or occlusive lesions, surgical revascularization or percutaneous transluminal angioplasty (PTA) with stenting is often necessary (7).

Takayashu's arteritis is associated with increased mortality. Previous research has shown that survival for 10 years is 97%, 15 years 85%, and 20 years 75% (4).

The aim of the research was to show the clinical characteristics, applied diagnostic and therapeutic procedures in a patient with Takayashu's arteritis, to compare them with the findings of patients with Takayashu's arteritis in other studies and to show the latest knowledge about this disease.

Presentation of the patient

37-year-old patient, at the end of September 2021, comes to the doctor for the first time when she states that she occasionally feels unable to breathe to the full extent of her lungs

and that she has a feeling that her heart is racing and skipping. A little later, in mid-October 2021, at two specialist examinations of a rheumatologist, she states that since July 2021 she has had extreme fatigue, tingling and discomfort in her legs, acceleration of heart rate and heart palpitations. She states that for the past two years she has occasionally had a feeling of palpitations, and since July 2021. the complaints have become more frequent. Since September 2021. she noticed that she could not measure her blood pressure, which was normally around 110/70 mmHg. In November 2021. the patient reported rapid fatigue and loss of strength in her left hand. Since January 2022. she has had a stabbing sensation in her chest when exposed to cold air, a tingling sensation, and an uncomfortable pain in her legs.

Personal and family history: The patient denies previous illnesses. There were no similar or other diseases significant for heredity in the family.

Physical examination showed that the findings on the heart and lungs were normal. Audible murmurs above both carotid arteries. The pulse of the right radial artery is very weak, and the pulse of the left radial artery is not palpable. Weakened pulses on the left tibial artery and the left popliteal artery. The pulses of both femoral arteries are properly palpated. During the month of November, during the examination, the pulses on both radial arteries and the pulses on both brachialis arteries are not palpable. Unmeasurable blood pressure bilaterally.

In laboratory analyzes performed at the end of September 2021, positive, non-specific indicators of inflammation were found: increased sedimentation of erythrocytes 38 mm/1h and increased level of C reactive protein (CRP) 19.7 mg/L.

The patient immediately underwent diagnostic examinations. First, color Doppler echosonography of the blood vessels of the neck was performed, which showed the presence of significant stenosis of the left 75–90% and the right 70–85% of the common carotid artery (ACC). Both ACCs have almost uniformly thickened walls in their proximal segments ("macaroni sign"), which leads to 70% stenoses (Figure 1). Significant stenosis of the subclavian arteries was found on both sides. The ultrasound findings indicated the existence of Takayashu's arteritis in the patient, so further diagnostics were continued.

After the ultrasound examination, a computerized tomography (CT) angiography of the head and neck was performed with the finding: The right ACC was affected throughout its course by a concentric tubular lesion with a reduced lumen of up to 60%. The right subclavian artery is of the fusiform type, it is narrowed by a concentric lesion about 30% to the vertebral artery, and after it, tubular, in a length of about 1.5 cm with a reduced lumen over 90%. The left ACC is

proximally in the longer segment of the concentrically tubular reduced lumen with the greatest stenosis over 65%. The left internal carotid artery (ACI) is after the bulb, eccentrically narrowed by a mixed plaque up to 50%. The left subclavian artery is, right after the separation of the vertebral artery, reduced lumen over 90% in a length greater than 2.5 cm.

Positron emission tomography of the whole body with anatomical localization (18 F-FDG PET/CT) was performed then with the finding: Increased accumulation of FDG is shown in the wall of both common carotid arteries, more intensively on the left. Moderately increased FDG accumulation is observed in the initial parts of both subclavia. FDG accumulation was discretely increased at the level of the wall of the aortic arch and the initial part of the descending aorta. The finding indicated an FDG-active underlying disease (Figure 2).

During October and November 2021 and January 2022, the patient underwent three echocardiographic examinations and all three showed normal findings on the heart.

Two EKGs performed in October 2021 showed normal findings with sinus rhythm, without ST and T segment changes. An EKG performed in November registered the existence of right bundle branch block.

Due to significant narrowing of the blood vessels, a vascular surgeon was consulted. Vascular conciliation set the indication for percutaneous transluminal angioplasty (PTA). The patient underwent balloon dilatation and stent implantation in the right subclavian artery.

Before the complete diagnosis, the patient occasionally used non-steroidal anti-inflammatory drugs, and after the diagnosis and the 18 F-FDG

PET/CT performed and the findings that showed FDG active disease, therapy with corticosteroids and immunosuppressants was started.

In April 2022, a control CT scan of the blood vessels of the neck was performed with the following findings: left ACC circumferentially narrowed in the proximal and medial segments by 40%, and the left subclavian artery postvertebrally narrowed by 90%; right ACC and right subclavian artery are without significant narrowing. Control CT angiography showed, after five months of treatment with corticosteroids and immunosuppressants, significant improvements, so the therapy was continued.

In September 2022, a control PET CT with FDG was performed, which showed that, unlike the previous PET CT examination in November 2021, the common carotid arteries and subclavian arteries did not show increased accumulation of FDG, i.e. that the previously described zones of increased glucose metabolism in the blood vessel walls are not showing in the moment of the exam (Figure 3).

The criteria of the American College of Rheumatology (1) were used for the clinical diagnosis of Takayashu arteritis, the criteria of the International Takayashu's Conference from 1994 were used for the angiographic classification, and the classification given by Ishikawa was used for the clinical classification of Takayashu's arteritis (8, 9).

According to the criteria for establishing the diagnosis of Takayashu's arteritis of the American College of Rheumatology, the patient meets 5 out of 6 criteria, and according to the angiographic and clinical classification, she belongs to Type I.

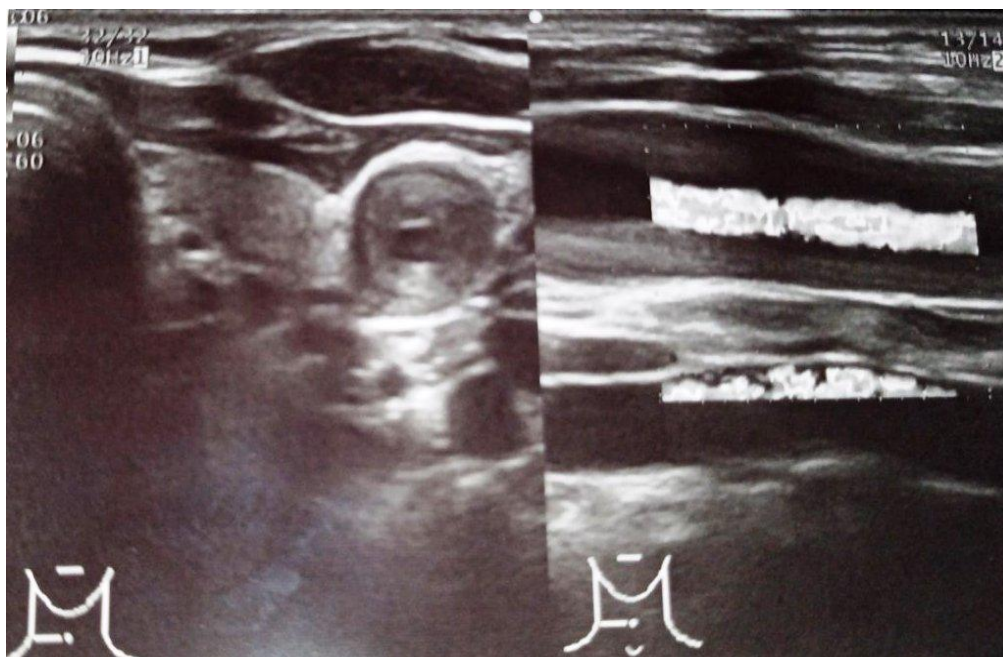


Figure 1. Ultrasonography of the left common carotid artery on transverse and longitudinal section – „Macaroni sign“



Figure 2. PET/CT with fluorodeoxyglucose – first examination



Figure 3. PET/CT with fluorodeoxyglucose – control examination after 10 months from the first examination

Discussion

Nowadays, it is accepted that the onset of Takayashu's arteritis is based on immunopathogenetic mechanisms with the primary role of autoimmunity and inflammation, and that both humoral and cellular immunity play a role in this (1). The initial agent to initiate the immune response is unknown, but it is capable of inducing an immune response directed at the walls of large arteries, where severe vascular damage can occur (1).

Takayashu's arteritis was suspected in our patient after an ultrasound examination of the carotid and subclavian arteries with findings of significant lesions on these arteries. Ultrasound examination showed the existence of a characteristic thickening of the peripheral arterial wall of both common carotid arteries, as a "macaroni", a diffusely thickened intimo-medial complex that arose as a result of chronic and persistent vascular inflammation that led to thickening of the adventitia and intimomedial hyperplasia due to cellular infiltrates (2). The "Macaroni sign" is pathognomonic for Takayashu's arteritis and studies have shown that it is present in 80.0% to 100% of patients (10, 11).

The presence of the "macaroni sign" on the ultrasound examination of the carotid arteries, not only significantly indicates Takayashu's arteritis, but also confirms the usefulness of ultrasound in its diagnosis. This is supported by studies that have shown that ultrasonography is more sensitive and superior in detecting this characteristic thickening of the intima-media complex in patients with Takayashu's arteritis, compared to contrast angiography, which showed carotid lesions in about 56.0% of patients and which is usually used to establish a definitive diagnosis of this disease. It is believed that angiography can show narrowing of the lumen and the degree of narrowing, but ultrasound is a better way to assess the vessel wall (2). However, there are opinions that Doppler sonography can detect stenosis of the affected arteries, but that it is non-specific for Takayashu's arteritis (12, 13).

According to angiographic and clinical classification, the patient belonged to Type I, which indicates relatively favorable vascular lesions and rare serious complications. Earlier studies showed that the frequency of type I in our population of patients with Takayashu's arteritis was the highest and was 50.0% (14).

It has been shown that the prevalence of type I is more common in women and type V in men (1), which correlates with the findings of some studies that women have more frequent lesions affecting the aortic arch and its branches, while in men, the abdominal aorta is much more often involved.

This difference in frequency may also be the result of selection of patients in different stages of Takayashu's arteritis development. Because Takayashu's arteritis is a chronic inflammatory disease, patients more often have type I in the

early stage of the disease, while type V can be seen in the late stage (15).

The patient had significant bilateral ACC and subclavian stenoses, with the lesions of the left ACC and left subclavian being more significant, which is in accordance to earlier findings that showed that the subclavian arteries, the left more than the right, were most often affected, followed by the ACC, also the left more than the right (16).

The frequency of carotid artery lesions, in different studies, ranges from 25.6% to 79.1% and subclavian from 20.9% to 79.8% (17).

The high prevalence of affection of the left branches of the aortic arch is in correlation with the hypothesis (9) that in Takayashu arteritis the arterial lesions begin in the left subclavian and then spread to other locations (18).

Stenosis of the left subclavian was also the most common in our population and was found in 88% of patients.

Our patient fulfill the first criteria of the American College for the diagnosis of Takayashu's arteritis because she was less than 40 years old when her disease was diagnosed. According to numerous studies, the average age of patients at diagnosis of Takayashu's arteritis ranged from 20.5 to 45.4 years. In our population, the average age at diagnosis of Takayashu's arteritis is 43.9 years. Recent studies conducted in different populations indicate that the proportion of patients older than 40 years, at the beginning of the disease, varies from 9% to 32% (19, 20).

It is accepted that the diagnosis of Takayashu's arteritis can be established, in persons younger than 50 years, if there are characteristic radiological and ultrasound lesions of large-caliber arteries without arguments for another vascular cause (4).

The much higher frequency of Takayashu's arteritis in women and younger age indicates that one of the reasons for this may be hyperestrogenism as one of the presumed causative factors of this vasculitis, and this is supported by the findings that most young women with Takayashu's arteritis have increased urinary excretion of estrogen in comparison with healthy persons of the same age (21).

There are difficulties in the early diagnosis of Takayashu's arteritis due to the frequent absence of disease activity and clinical symptoms, in the phase of remission, which explains the delay in diagnosing the disease from several months to 4 years (1).

Our patient had a negligible time delay in establishing the diagnosis thanks to an early ultrasound examination of the blood vessels when significant stenoses of the carotid and subclavian arteries with the "macaroni sign" were observed.

Symptoms of Takayashu's arteritis are often vague and nonspecific, and may be absent. The patient had no pronounced general symptoms at the time of presentation, which is not unusual because many studies find that general symptoms were absent in 34% to 57% of patients. From the clinical manifestations of the disease, the patient

had murmurs over the carotid arteries and weakened pulse, i.e. loss of pulse, over the radial arteries. Research has shown that the frequency of murmurs over the carotid arteries is observed in 62.5% to 70% of the patients, and the weakened pulse over the radial arteries from 34.8% to 88% (22, 23).

The patient had, at the beginning of the presentation, high sedimentation rate and a high level of CRP. Previous studies have shown that the inflammatory syndrome is present in the early stage of Takayashu's arteritis in 71% to 85% of sufferers. Erythrocyte sedimentation rate in the acute phase of Takayashu's disease increased in 53.7% to 89.7%, and high CRP level in 79.1% (24, 25).

Due to the lack of a specific serum marker for Takayashu arteritis (22), the inflammatory syndrome remains a significant but imperfect reflection of the activity of the underlying disease, as active disease is possible in the absence of the inflammatory syndrome in approximately 30% of patients (4). Elevated erythrocyte sedimentation rate is a strong indicator of an underlying inflammatory process such as Takayashu's vasculitis. However, erythrocyte sedimentation rates within the normal range should not rule out the existence of Takayashu's arteritis (18) because vascular damage can progress even in the absence of systemic inflammatory changes.

The treatment of our patient was started with the simultaneous administration of corticosteroids and immunosuppressants, and the goals of the treatment were to control active inflammation, minimize arterial damage and the

development of vascular complications, which was achieved with the treatment, because control CT-angiography showed that regression of lesions occurred in some vessels, while further progression was stopped in others and control PET/CT confirmed that there is no longer FDG active disease (26).

Corticosteroid therapy is effective when the disease is diagnosed early, and remission can be achieved in 25% to 50% of cases with the use of corticosteroids alone. The use of immunosuppressants as a first-line treatment in order to reduce the use of corticosteroids has shown good results. The addition of immunosuppressants to corticosteroids allows remission in 50% to 80% of corticosteroid-resistant cases (4).

The patient had symptomatic stenotic lesions, which required percutaneous angioplasty with stent placement (7).

Conclusion

Ultrasonography is an effective and non-invasive method for early detection of Takayashu's arteritis, and the presence of the "macaroni sign" on an ultrasound examination of the carotid arteries significantly indicates Takayashu's arteritis.

Positron emission tomography angiography is significant and effective in determining and identifying disease activity in the vascular wall. Combined therapy with corticosteroids and immunosuppressive drugs is successful in preventing further progression of the disease.

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Prikaz slučaja

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**KLINIČKE I ANGIOGRAFSKE KARAKTERISTIKE
TAKAYASUOVOG ARTERITISA: PRIKAZ BOLESNIKA***Dušan Miljković¹, Slađana Todorović¹, Miloslav Jovanović²*¹Dom zdravlja „Dr Vlastimir Godić“, Varvarin, Srbija²Farmaceutska kompanija „Alkaloid“, Skoplje, Republika Severna Makedonija

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Takayasuov arteritis je hroničan, imunoposredovan vaskulitis velikih krvnih sudova, koji se obično javlja kod bolesnika mlađih od 50 godina i prvenstveno zahvata aortu i njene glavne grane. Među obolelima preovladavaju žene. Prikazana je bolesnica sa Takayasuovim arteritisom koja se prvi put javila lekaru zbog umora, palpitacija i ubrzanog rada srca. Kliničkim pregledom ustanovljeni su, iznad obeju karotidnih arterija, čujni šumovi i veoma oslabljen puls desne arterije radialis, a puls leve radialne arterije nije se mogao izmeriti palpacijom. Laboratorijskim analizama utvrđeni su povišena sedimentacija eritrocita i povišen nivo C-reaktivnog proteina. Dijagnoza bolesti potvrđena je ultrazvučnim doplerom krvnih sudova, kompjuterizovanom tomografijom i angiografijom (engl. *computed tomography angiography* – CTA) i pozitronskom emisionom tomografijom (engl. *fluorine-18 fluorodeoxyglucose positron emission tomography* – 18 F-FDG PET/CT). Bolesnica je ispunjavala pet od šest kriterijuma Američkog koledža za reumatologiju za postavljanje kliničke dijagnoze Takayasuovog arteritisa i, prema angiografskoj i kliničkoj klasifikaciji Takayasuovog arteritisa, pripadala Tipu I. Bolesnica je lečena kortikosteroidima, imunosupresivima i perkutanom transluminalnom angioplastikom.

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Ključne reči: Takayasuov arteritis, znak makarona, dopler krvnih sudova, višeslojna kompjuterizovana tomografija, pozitronska emisiona tomografija / kompjuterizovana tomografija

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