

TAKAYASU ARTERITIS: NEW TRENDS IN SURGICAL APPROACH – CASE PRESENTATION

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Summary

Takayasu arteritis (TA) is defined as a rare chronic granulomatous panarteritis that classically involves segments of large arteries such as the aortic arch. The aim of this report is to present our recent experience in diagnosis and treatment of TA and to provide aspects of surgical strategy for inflammatory aneurysms caused by TA. We present the case of a 36-year-old Caucasian female admitted to our clinic with low effort dyspnea, fatigability, palpitations, sweats, malaise and light-headedness. The medical history revealed a history of treated tuberculosis, anemia, arterial hypertension, chronic inflammatory syndrome, aortic insufficiency, and anterior mitral valve prolapse. Echocardiography revealed grade III-IV aortic regurgitation, grade I-II mitral regurgitation, a dilated ascending aorta and mild systolic dysfunction. CT angiography revealed an aneurysmal dilatation of the ascending aorta. Surgical treatment was mandatory, and intraoperative, the surgeon noted a diffuse thickening of the aortic wall and suspected TA, further confirmed by histopathological examination. The tricuspid aortic valve was excised and a composite graft with a biological valve and an aortic conduit were implanted on patient's request. Postoperative course was uneventful and the patient was discharged from the hospital on the 10th postoperative day, and directed towards Rheumatology Clinic for medical treatment. A multidisciplinary approach to the diagnosis and management of TA patients is essential to a satisfactory outcome.

Key words: Takayasu's arteritis, imaging diagnosis, intimal aortic thickening, aortic valve replacement

Rezumat. Tendințe actuale ale abordului chirurgical în arterita Takayasu – prezentare de caz

Arterita Takayasu (AT) reprezintă o formă rară de panarterită granulomatoasă care afectează în principal aorta și arterele mari. Scopul studiului prezent este de a prezenta experiența recentă a Institutului de Boli Cardiovasculare din Iași privind diagnosticul și strategia terapeutică chirurgicală într-un caz de dilatație anevrismală a aortei ascendente determinată de AT. Autorii prezintă cazul unei paciente de 34 ani spitalizată pentru dispnee la eforturi mici, fatigabilitate, palpitații, transpirații, astenie și cefalee ușoară. Istoricul medical relevă antecedente de tuberculoză pulmonară tratată, anemie, hipertensiune arterială, sindrom inflamator persistent, insuficiență aortică și prolaps de valvă mitrală anterioară. Examenul ecocardiografic evidențiază regurgitare aortică grad III-IV, regurgitare mitrală grad I-II, dilatație a aortei ascendente și disfuncție sistolică ușoară. Angiografia computer tomografică (CT) confirmă dilatația anevrismală a aortei ascendente și obiectivează modificări sugestive de vasculită la nivelul aortei ascendente, crossei aortice și ramurilor mari emergente din crosă. Severitatea dilatației aortei ascendente și a regurgitării valvulare aortice impun abord chirurgical. Intraoperator, se identifică îngroșarea difuză a peretelui aortic și se suspectează AT, diagnostic confirmat ulterior anatomopatologic. Se excizează valva aortică, tricuspida, și se plasează un graft compozit alcătuit dintr-o proteză valvulară biologică (la solicitarea pacientei) și un conduct aortic, cu evoluție postoperatorie favorabilă, pacienta fiind externată a 10-a zi postoperator și direcționată spre Clinica de Reumatologie în vederea tratamentului medical. În concluzie, AT impune abord multidisciplinar în vederea stabilirii unei conduite diagnostice și terapeutice medico-chirurgicale optime, conform ghidurilor în vigoare.

Cuvinte-cheie: arterită Takayasu, diagnostic imagistic, aortită, protezare aortică

Резюме. Современные направления хирургического лечения болезни Такаясу – клинический случай

Болезнь Такаясу (БТ) – аутоиммунное заболевание, характеризующееся хроническим воспалением крупных артерий, преимущественно аорты и её ветвей. Цель настоящей работы заключается в ознакомлении с недавним опытом Института сердечно-сосудистых заболеваний г. Яссы в диагностике и тактике лечения аневризмы восходящей аорты, обусловленной БТ. Коллектив авторов представляет клинический случай пациентки 34-х лет, госпитализированной со следующими симптомами: одышка при небольших нагрузках, повышенная утомляемость, сердцебиение, лёгкие головные боли, повышенная потливость. Проведённый анамнез выявил: излечённый туберкулёз лёгких, анемию, артериальную гипертензию, персистентный воспалительный синдром, недостаточность аортального клапана и пролапс передней створки митрального клапана. Эхокардиографическое исследование выявило регургитацию аортального клапана III-IV ст., недостаточность митрального клапана I-II ст., расширение восходящей части грудной аорты и некоторое снижение систолической функции. Компьютерная томографическая ангиография (КТА) подтвердила аневризматическое расширение восходящей аорты с обнаружением сопутствующих признаков васкулита восходящей аорты, дуги аорты и её ветвей. Опираясь на полученные результаты исследований принято решение о хирургическом лечении. Во время оперативного вмешательства обнаружено утолщение стенки аорты, с подозрением на БТ, позже подтверждённым результатами анатомопатологического исследования. Производится протезирование клапана аорты и восходящей аорты комбинированным протезом, состоящим из биологического клапана аорты (по желанию пациентки) и линейным сосудистым протезом. Пост

операционный период без осложнений. На 10-ый день пациентка переведена в клинику ревматологии для прохождения последующего этапа лечения. Выводы: БТ требует поликлинического подхода для принятия оптимального решения в плане диагностики и лечения, согласно современным рекомендациям.

Ключевые слова: утолщение интимы, болезнь Такаясу, замена аортального клапана

Introduction

Takayasu arteritis (TA) also known as “pulseless disease”, occlusive thromboangiopathy, or Martorell syndrome, is defined as a rare chronic granulomatous panarteritis that classically involves segments of large arteries such as the aortic arch [1]. In 1/3 of the cases the remainder of the aorta and its branches, and the pulmonary arteries are also affected [2]. The histopathological examination reveals, in most cases an irregular adventitial thickening with intimal wrinkling, fibrosis, stenosis, thrombus formation and intimal hyperplasia [3]. Arterial acute inflammation can lead to media degeneration, with aneurysm formation (25% of cases in the studied literature) [3-6]. Coronary, subclavian and renal arteries may be equally affected, associated with considerable morbidity and premature mortality amongst young female patients.

This paper reports the case of a young woman with a history of tuberculosis, arterial hypertension and infertility, which presented aneurysmal ascending aorta and aortic regurgitation due to TA and underwent surgical repair of the aortic valve and ascending aorta.

Case presentation

A 36-year-old Caucasian female was admitted to our clinic with low effort dyspnea, fatigability, palpitations, sweats, malaise, and light headaches. The medical history of the patient has revealed a history of tuberculosis (treated 10 years ago), anemia, arterial hypertension and chronic, unexplained, inflammatory syndrome (diagnosed 6 years ago), aortic regurgitation and anterior mitral valve prolapse (diagnosed

2 years ago). Cardiovascular examination revealed tachycardia (115 beats/minute), weak radial pulse, holosystolic (regurgitant) heart murmur in the aortic area, irradiating to both carotid arteries. Based on the EKG left ventricular hypertrophy was suspected. Laboratory tests results sustained an inflammatory syndrome with a C-reactive protein of 29 mg/dl.

Echocardiography diagnosed a grade III-IV aortic insufficiency, grade I-II mitral insufficiency, a dilated ascending aorta (50 mm), an aortic annulus diameter of 24 mm, a tricuspid aortic valve, and mild systolic dysfunction of the left ventricle.

CT angiography revealed an aneurysmal dilatation of the ascending aorta (51 mm at the level of the right pulmonary artery, 33 mm proximal to the brachiocephalic arterial trunk, gradually decreasing to 28 mm at the level of the first transverse segment and 26 mm at the level of the second transverse segment), and thickening of the walls of the aortic arch and its branches (fig. 1).

A gross unspecific thickening (up to 6 mm) of the walls of the aorta (ascending and arch), brachiocephalic trunk, subclavian arteries, and common carotid arteries was identified (fig. 2).

Right subclavian artery registered a long, severe stenosis after the origin of the right vertebral artery, with near occlusion of the proximal axillary artery, and retrograde filling of distal axillary artery through collaterals. Left subclavian artery was also severely involved (4 mm permeable lumen) (fig. 3).

Because there was noticed a severe thickening of the common carotid walls and a dilation of the right



Fig. 1. CT showing severe thickening of aortic walls



Fig. 2. CT showing thickening of aortic and left subclavian artery walls

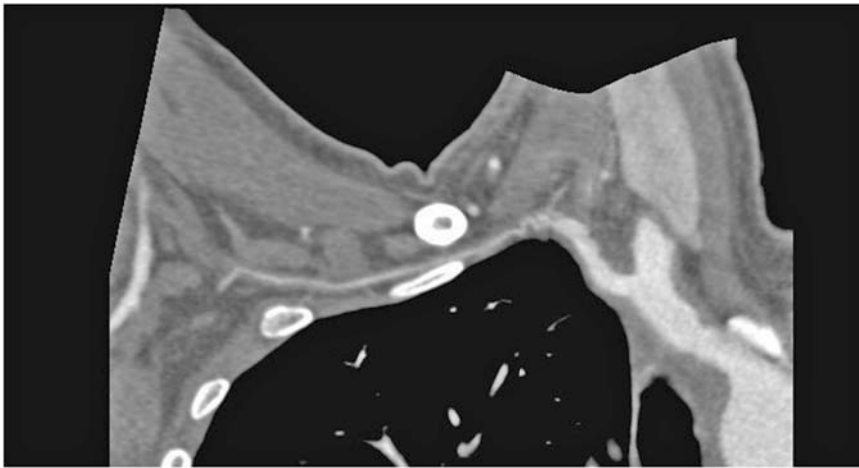


Fig. 3. CT showing severe stenosis of right subclavian artery with distal occlusion

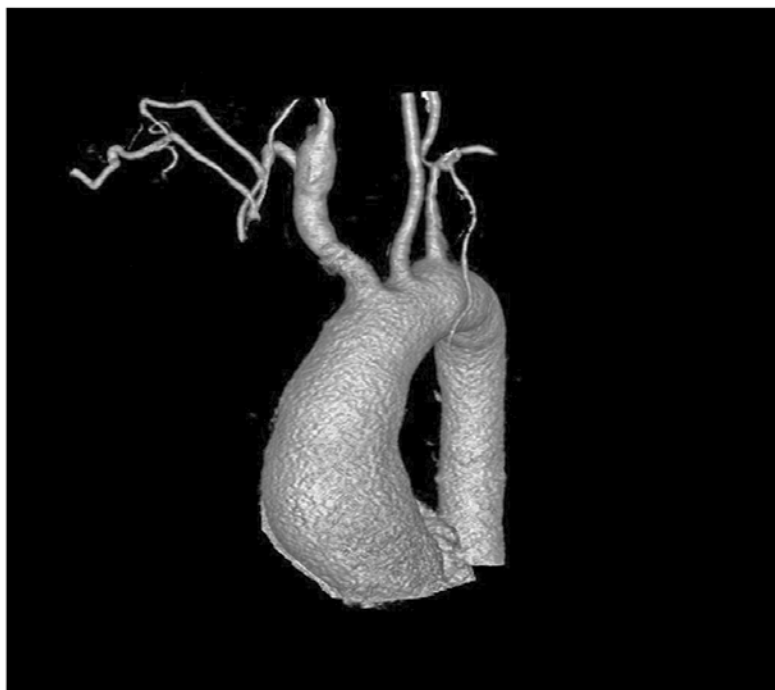


Fig. 4. CT showing prestenotic dilatation of the right common carotid artery

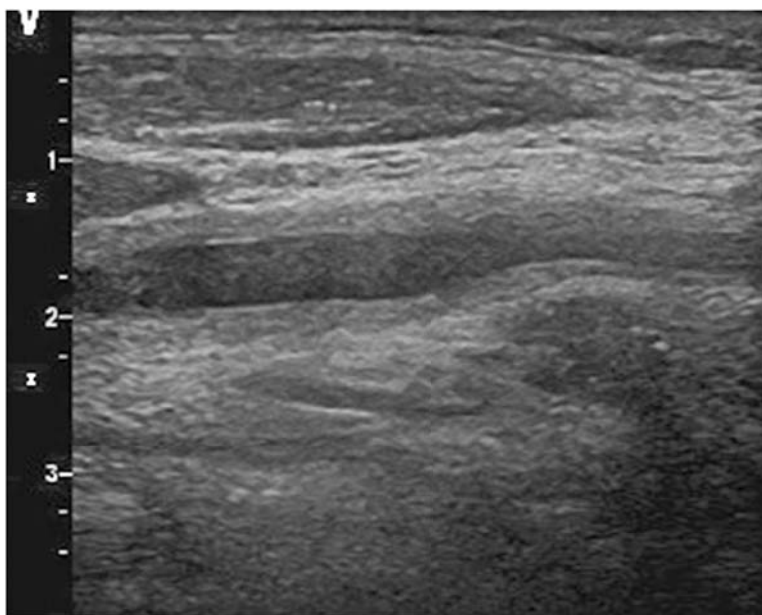


Fig. 5. Doppler ultrasound showing narrowing of the left common carotid artery

common carotid artery, a Doppler ultrasound examination was indicated (fig. 4).

Doppler ultrasound revealed a 50-69% stenosis (PSV 163 cm/s) of the right common carotid artery with prestenotic dilatation and a less than 50% stenosis of the left common carotid artery (PSV 113 cm/s). Both carotid bifurcations and proximal internal carotid arteries were involved, without significant stenosis (fig. 5).

A non-specific arteritis was evoked based on preoperative imaging. Because of the important aortic regurgitation and aneurysmal dilatation of the ascending aorta, surgical treatment was considered mandatory. Surgery was performed through median sternotomy. Intraoperative, the surgeons noted a significantly dilated aortic root and diffuse thickening of the aortic wall (5 mm), and suspected Takayasu arteritis, suspicion further confirmed through histopathological examination. The tricuspid aortic valve was excised and a composite graft with ascending aorta replacement using an aortic conduit (diameter 26 mm, usable length 50 cm, Gelweave™ manufactured by Vascutek Ltd, Scotland) attached with a prosthetic aortic valve (a 23 mm biological valve (Edwards Lifesciences model 2980) was implanted, on patient's special request by performing a modified White procedure.

The pathological specimen exhibited a panarteritis characterized by severe thickening of the adventitia, media, and intima, and residual inflammatory changes including lymphocyte infiltration, thus confirming the diagnosis of Takayasu's arteritis. Postoperative course was uneventful and the patient was discharged from the hospital on the 10th postoperative day, and directed towards a Rheumatology Cli-

nic for medical treatment. The patient presented for one-month control. The echocardiographical examination showed normal results and she was doing well in normal daily activities.

Discussions

Epidemiology. Takayasu, a Japanese professor of ophthalmology at Kanazawa University Japan, first reported TA in 1905 [7]. TA is mainly diagnosed in young women (female:male ratio of 8:1) with a typical onset around the age of 25-30 years. Some hospital based studies report an incidence of 1-2 cases per million, however available data regarding its real incidence and prevalence are yet limited both in Romania and worldwide [8].

Etiology and Pathogenesis. The etiology of TA is still uncertain, same as its pathogenic course. In 1996, a hypothesis has been developed where 65kDa heat-shock protein (HSP) in the aortic tissue is stimulated by unknown stimuli inducing a major histocompatibility class I chain-related A (MICA) located on the vascular cells, producing hemodynamic stress [9]. Previous studies have suggested that there is an increased risk for some immune-mediated diseases to develop after tuberculosis, but the question of which disorder came first is difficult to disentangle [10]. Our patient was treated for tuberculosis 10 years ago and was diagnosed with a chronic, unexplained, inflammatory syndrome 6 years ago, two important arguments in the favor of the hypothesis that tuberculosis is involved in the determinism of TA. Tuberculosis is an important differential diagnosis (tuberculous aortitis) and a possible etiological factor for TA, especially in endemic areas, such as Moldavia, but we lack information (complete medical history with occurrence

dates) in order to determine the causality relation of the two diseases.

Histopathology. The gross morphologic intraoperative examination revealed irregular thickening of the aortic vessel and its branches wall with intimal wrinkling (fig. 6).

Nasu provided a detailed review concerning the pathological aspects of TA [11]. In his opinion, the main pathological finding is severe destruction of medial elastic fibers that maintain the strength of the aortic wall. In the early and active inflammatory phases, granulomatous inflammation is present, with various cellular infiltrations in the adventitia and the outer part of the media, along with marked inflammation of the *vasa vasorum*. Subsequently, in the chronic stage, severe intimal thickening occurs in the areas that overlie granulomatous and fibrotic lesions in the media and adventitia. Even in this stage, some patients present residual inflammatory changes including lymphocyte infiltration, as was the case of our patient. Pathological specimens of aortic valve leaflets resected during surgery exhibited no evidence of inflammation but presented severe secondary changes, such as curling and thickening of the free margins of the valve leaflets.

Presentation and differential diagnosis. Being a systemic disorder, TA affects multiple organs thus representing a challenge for physicians of different specialties. TA clinical manifestations range from asymptomatic disease, diagnosed on the absence of the pulse or presence of pathological heart murmurs, to catastrophic neurological impairment, according to the two phase's development of the disease. TA presents an early and sometimes prolonged *active*

phase and a late, *chronic phase*, accompanied or not by previous inflammatory syndrome history. Patients with TA are usually admitted for non-specific systemic symptoms like fatigue, fever, arthralgia, weight loss, malaise, weakness, night sweats and vision changes. In our case the symptoms were nonspecific, major clinical features being represented by high blood pressure and weak radial pulse with coldness or numbness of the fingers. Currently, there is no single diagnostic test available, but nonspecific features like fever, fatigue, malaise, arthralgia and night sweats are suggestive for a positive diagnosis (table 1) [12].

Table 1. Criteria to Diagnose Takayasu's Arteritis (1990 ACR criteria) [12]:

1. Age under 40 at disease onset (development of symptoms or findings related to Takayasu arteritis at age <40 years);
2. Claudication of extremities (Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities);
3. Decreased brachial artery pulse (Decreased pulsation of 1 or both brachial arteries);
4. Blood pressure difference more than 10 mmHg between arms;
5. Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta;
6. Angiogram abnormalities: occlusion or narrowing in aorta or its main branches Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not caused by arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental.

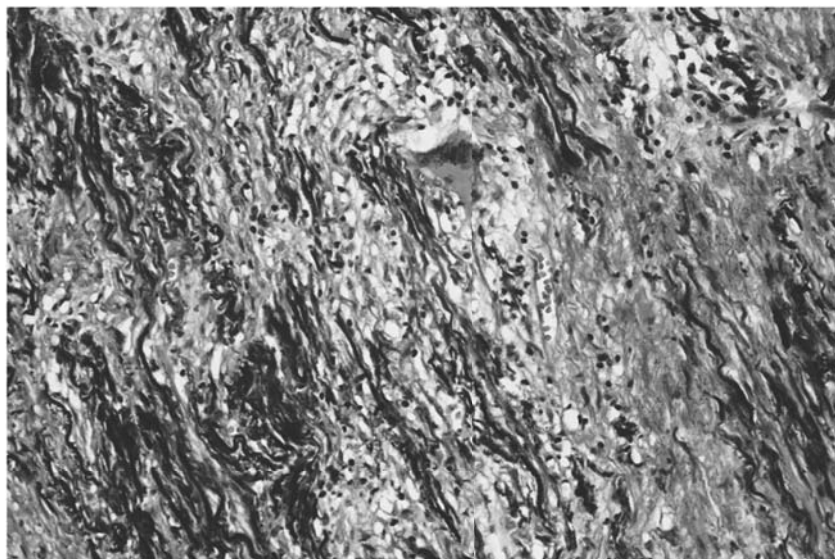


Fig. 6. Scar stage of Takayasu arteritis – adventitial fibrosis, medial elastic fibers destruction (Elastica van Gieson stain x40)

A diagnosis of Takayasu arteritis requires that at least 3 of the 6 criteria are met. TA may be suspected based on clinical presentation and medical imaging. Histopathological confirmation can be obtained for patients undergoing vascular surgery. Given the non-specific clinical symptoms, diagnosis is often delayed and patients receive inappropriate symptomatic treatment.

Differential diagnosis may include certain congenital or acquired conditions associated with aneurysmal aortic dilatation (Marfan syndrome, Ehler-Danlos syndrome, Loeys-Dietz syndrome, syphilis), tuberculosis, autoimmune conditions associated with vasculitis (systemic lupus erythematosus, giant cells arteritis, Cogan syndrome, Behçet's disease, Churg-Strauss disease, sarcoidosis, polyarteritis nodosa), neurofibromatosis and idiopathic aneurysms. These disorders are not associated with stenotic lesions of large vessels, which is a common finding in TA.

Paraclinical diagnosis. Laboratory test results are usually non-specific in TA, such as a raised erythrocyte sedimentation rate (ESR) in 50% cases, increased serum C-reactive protein (CRP) and normocytic normochromic anemia, reflecting an underlying inflammatory process. In our case, laboratory tests results revealed increased C-reactive protein levels (29 mg/dl) and mild anemia (hemoglobin 9,60g/dL). Serum anti-endothelial cell antibodies (AECA) have also been reported in patients with TA by some researchers but their role is still uncertain [7]. Positive diagnosis is largely based on symptoms, and clinical and imaging findings (echocardiography, CT, MRI, angiography) like arterial stenosis, occlusion, aneurysmal dilatation, and wall thickening [13].

Treatment and prognosis. The aim of TA treatment is to control the disease activity and to preserve vascular competence, with minimal long-term side effects, but the management can be problematic [14]. Medical treatment of TA is based on anti-inflammatory and immunosuppressive therapy, most of the cases responding to high-dose oral prednisolone (1-2 mg/kg/day). Due to the delay in diagnosis and the severity of the aortic involvement, our patient was firstly treated surgically (rates of primary surgical interventions varies in literature from 12 to 70%) [15]. Surgery is recommended at a time of quiescent disease in order to avoid complications, like secondary stenosis, anastomotic failure, thrombosis, hemorrhage, and infection. Vascular surgery should be avoided in active inflammatory phase, but certain cases with uncontrolled hypertension, severe symptomatic coronary artery or cerebrovascular disease, severe aortic regurgitation or coarctation, stenotic or occlusive lesions resulting in critical limb ischemia, and

aneurysms at high risk of rupture urge for immediate surgical repair.

Miyata et al. demonstrated that surgery increases the long-term survival of patients with stage 2 and 3 TA (major complication and progressive disease), based on prognostic classification by Ishikawa (table 2), while conversely survival is decreased in stage 1 TA patients (no major complications and no evidence of progressive disease) due to surgery-related complications [16].

Table 2

Ishikawa clinical classification of Takayasu arteritis (16)

Group	Clinical features
I	Uncomplicated disease, with or without pulmonary artery involvement
IIA	Mild/moderate single complication together with uncomplicated disease
IIB	Severe single complication together with uncomplicated disease
III	Two or more complications together with uncomplicated disease

There is a chance of some uncertainty regarding the onset and course of the disease, a poor correlation between clinical assessment and disease activity, poor disease activity markers in peripheral blood or a lack of useful treatment in up to 25% of patients with progressive disease [14]. Overall, surgical outcomes have improved over time, aided by advances in surgical techniques and technology as well as improvements in preoperative optimization and peri- and postoperative care [15].

Regarding the medical treatment of TA, the European League Against Rheumatism (EULAR) recommends an initial high-dose glucocorticoid therapy (prednisolone 1 mg/kg/day with a maximum of 60 mg/day) for a month in order to induce remission followed by a gradual tapering up to 10-15 mg/day at 3 months. An alternate day therapy is not recommended as it can lead to a relapse [16].

Case particularities

Hypertension associated with weak peripheral pulse and a chronic inflammatory syndrome represents important differential diagnosis clues. Ascending aorta dilatation with subsequent aortic valve regurgitation or aortic dissection rather than medium/small vessels stenosis are the major complications of TA. Severe aortic regurgitation due to ascending aorta dilatation, like the case of our patient, is usually associated with significant morbidity, ranging from pulmonary edema to refractory heart failure and cardiogenic shock. In such conditions surgery is compulsive (table 3) [17]. Miyata et al. 12 reported that

the incidence of anastomotic aneurysm in Takayasu arteritis is 8.5% [15].

Table 3. Current ACC/AHA guidelines, aortic valve surgery recommendations [17]

- Patient is symptomatic;
- Patient is asymptomatic, with a resting EF $\leq 55\%$;
- Patient is asymptomatic, with LV dilation (LV end-systolic dimension [LVESD] > 55 mm).

Given the severity of the aortic regurgitation and the degree of enlargement of the ascending aorta, the aortic valve was replaced at the same time with the aortic repair by performing a modified White's procedure that was successfully undertaken. These results may support the superiority of technical modification of the aortic valve replacement or modified Whites operation for effective treatment of patients with aortic insufficiency and ascending aorta aneurysmal dilatation, with aortic root preservation. Our patient, being a young female wishing a child, the issue of pregnancy was important. Due to the severity of her condition and the high probability of progressive valvular disease, we felt that concomitant valve replacement using a bioprosthesis instead of a mechanical one is appropriate. Positive diagnosis was mainly based on physician awareness, along with a high index of suspicion.

It is well documented that TA follows a cyclic course, including acute onset, subsequent chronic state with progressive deterioration, and periodical ex-

acerbation in some cases [8, 12]. Once diagnosed, a key limitation to optimal management is the relative lack of sensitive and accurate means for monitoring inflammatory activity (specific serological tests). The low prevalence of the condition makes it difficult to provide a standardized approach for diagnosis and treatment, particularly in Romania.

Being a systemic vasculopathy, TA can progress and cause vital organ ischemia, thus requiring long term follow up. The prognosis of TA improved in the last decade due to increasing usage and advance of noninvasive imaging methods, medical and surgical treatment. The five-years survival rate from the time of diagnosis ranges from 60 to 83% in the reviewed studies [13, 15, 17].

Conclusions

Current challenges of TA include lack of awareness concerning this condition, diagnosis delay due to unrecognized nonspecific symptoms, rapid progression and suboptimal methods for assessing disease activity. Besides imaging aspects, an age younger than 40, weak radial pulses, claudication, hypertension or blood pressure difference between the upper limbs and carotid or subclavian bruits are significant clues to the diagnosis of TA.

A multidisciplinary approach to the diagnosis and management of Takayasu arteritis patients is essential to a satisfactory outcome. Aggressive surgical treatment is recommended in cases with aortic dilatation and valvular regurgitation even if inflammation signs seem to be controlled. Long-term follow-up by non-invasive imaging methods is essential to moni-

Keypoints:

- TA is a very rare systemic disorder in the Romanian population;
- Tuberculosis is an important differential and possible aetiological factor for TA, especially in endemic geographical areas;
- Vascular involvement tends to be progressive, leading towards delays and challenges in establishing the clinical diagnosis.
 - Manifestations range from asymptomatic disease, found as a result of impalpable pulses or bruits, to catastrophic neurological and cardiovascular impairment;
 - The four most important complications for classification are Takayasu retinopathy, secondary hypertension, aortic regurgitation, and aneurysm formation, each being graded as mild/moderate or severe at the time of diagnosis;
 - Treatment should aim to control the disease activity and preserve vascular competence, with minimal long term side effects.
 - Aggressive surgical treatment is recommended for cases with aortic dilatation and valvular leakage even when inflammation signs appear to be controlled.
 - Due to varying clinical presentations and course of the disease, multidisciplinary approach is essential to achieve satisfactory patient outcomes.

ring disease activity and increasing the life expectancy of patients with TA.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Abbreviations

AVR: Aortic valve replacement;

CGR: Composite graft replacement;

CRP: C-reactive protein

LVED: left ventricle end-diastolic diameter

MICA: major histocompatibility class I chain-related A

Competing interests

The authors declare that they have no competing interests. All authors contributed equally to this work.

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