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TAKAYASU ARTERITIS – A SYSTEMATIC REVIEW

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Abstract. *Takayasu arteritis is a chronic, progressive, idiopathic, large-vessel vasculitis that affects the aorta, its main branches and the pulmonary arteries. It typically occurs in young Asian women but can be found in any ethnic group and in men. The disease is named after Mikito Takayasu, a Japanese ophthalmologist, who first described the arteriovenous anomalies in the retina of a patient with the disease in 1908. The etiopathogenesis is not known, but studies are being conducted regarding the immunological, infection and genetic aspects of the disease. Early during the course of the disease, inflammation of the involved arteries progresses, resulting in segmental stenosis, occlusion, dilatation and/or aneurysm. The clinical presentation of Takayasu arteritis varies depending on the blood vessels involved. Early symptoms are nonspecific, making the diagnosis difficult. Subsequently, arterial occlusions occur, producing more specific ischemic symptoms. Paucity of specific symptoms and laboratory biomarkers, as well as difficulties in assessing the disease activity and progression, make it often unrecognized at onset, and its activity is frequently underestimated. The diagnosis is usually confirmed by a combination of clinical manifestations, laboratory markers, diagnostic criteria and imaging methods. The purpose of this review is to address the current knowledge on pathogenesis, investigations, classification and management, and to emphasize the need for timely diagnosis, effective therapeutic intervention, and close monitoring of this disease.*

Key words: *vasculitis, Takayasu arteritis, pulseless disease*

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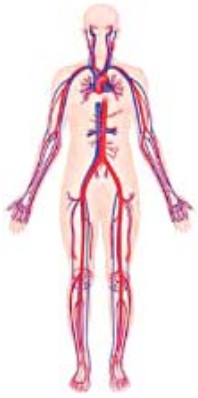
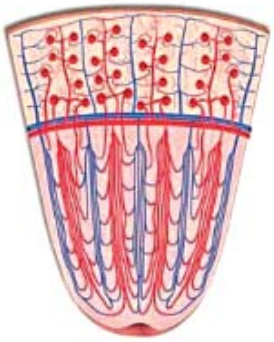
INTRODUCTION

The vasculitides are a heterogeneous group of diseases [1]. They are characterized by inflammatory cell infiltration and necrosis of the blood vessels walls leading to organ dysfunction.

The nomenclature and classification of the different types of vasculitis have been difficult and controversial for many decades. This is problematic for both the research on vasculitis as well as for the clinical care of patients with vasculitis. The 2012 International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC 2012) proposed names and definitions for the most common forms of vasculitis (Table 1) [2, 3].

Table 1. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

A. Large vessels	B. Medium vessels	C. Small vessels
Aorta and its major branches	Main visceral arteries and their initial branches	Intraparenchymal arteries, arterioles, capillaries
		

TAKAYASU ARTERITIS – DEFINITION, HISTORY, EPIDEMIOLOGY

Takayasu arteritis (TA) is an idiopathic, chronic, granulomatous, large-vessel arteritis that predominantly involves the aorta, its major branch arteries and (less frequently) the pulmonary arteries [4, 5, 6, 7, 8, 11]. The disease has been referred to with several different names in the past, such as aortic arch syndrome, pulseless disease, idiopathic aortitis, stenosing aortitis, aortoarteritis, and occlusive thromboarteriopathy [4].

The Italian pathologist Gian Battista Morgani is the first one to describe the TA. A century later, British doctors Davu J. and Savory W. also describe a clinical condition which resembles the disease. However, the first description of TA is usually attributed to MikitoTakayasu who presented a case of a 21-year-old woman with arteriovenous anastomosis surrounding the papilla on the eyeground. The abstract was published in 1908 in the Proceedings of the Japan Ophthalmology Society [6].

The overall rate is 2.6 per million [7]. Although the disease has a worldwide distribution, it is observed more frequently in Asian countries such as Japan, Korea, China, India, Thailand and Singapore. Approximately 80% of patients with Takayasu arteritis are women. However, the high female-to-male ratio seems to decrease west of Japan 8:1. In India the female-to-male ratio is as low as 1.6:1 [8].

ETIOLOGY AND PATHOGENESIS

The aetiology of Takayasu arteritis remains poorly understood. Several hypotheses are analysed, including:

1. The genetic hypothesis: association with the HLA complex (human leukocyte antigen). HLA associations are numerous and different according to the patients' ethnic background (HLA-B52 in Japanese, HLA-B5 have been described in patients with Asian and Mexican Mestizo background, HLA-A2, -A9, and -B35 in Arabs, HLA-DR4 in North American patients). Certain polymorphisms (rs12524487 and rs9366782) in HLA-B/MICA have been associated with TA or risk of ischemic brain disease in TA in a Chinese population. Additionally, a variant in the IL17F gene (rs763780) has been found to be protective against the development of TA [4].
2. The infection hypothesis

A pathogenic role for infection has been hypothesized by several investigators but supporting evidence has so far remained elusive or inconclusive. TA has been reported in HIV patients. A case of post-hepatitis B vaccination has been described. Similarly, the role of tuberculosis (TB) in TA is still controversial. Molecular mimicry between the mycobacterial 65-kDa heatshock protein (HSP) and human 65-kDa HSP has been suggested, which could elicit an immunologically-mediated cross-reaction and lead to an autoimmune response. Several authors have reported the presence of T cells reactive to mycobacterial 65-kDa HSP and its homologous human HSP, as well as serum IgG antibodies directed toward mycobacterial and human 65-kDa HSP, in patients with TA. Furthermore, the 65-kDa HSP has been isolated from the middle layer and vasa vasorum in aortic biopsies from patients with TA. Chauhan et al. demon-

strated circulating anti-aortic endothelial cell antibodies (AAECAs) that were directed against 60–65 kDa HSP in patients with TA. Sera from AAECA-positive TA patients induced expression of adhesion molecules and secretion of proinflammatory cytokines by aortic endothelial cells, which suggests a potential pathogenic role of these autoantibodies. Finally, the association between TB and TA seems to be much weaker in countries with a low prevalence of TB [4].

3. Immunological hypothesis

Both cell-mediated and humoral immune mechanisms lead to inflammation and tissue damage in TA. Both circulating anti-endothelial cell antibodies (AECA) and autoantibody-producing B cell infiltrates in inflamed vessels point to a role of humoral immunity. The question remains open whether these mechanisms are pathogenetic or an epiphenomenon. Hoyer et al. found a significant increase of newly generated plasmablasts in patients with active disease, suggesting a prominent role for B cells in the pathogenesis and supporting the use of anti-B cell therapies in TA. CD8-positive T cells, the main component of the inflammatory infiltrates in affected vessels, have been proposed as key mediators of vessel damage through the release of perforin and granzyme B. Circulating and tissue-infiltrating γδ T-cells have been reported to be expanded in TA patients during the active phases of the disease.

Immuno-pathogenesis of Takayasu arteritis: Dendritic cells in the adventitia expressing specific HLA molecules are activated by a so far unrecognized stimulus. Expression of the 65 kDa HSP in the aortic tissue might play a role in dendritic cell activation. These cells synthesize and release proinflammatory cytokines (such as IL-18) and homing chemokines that recruit T cells to the vessel wall and initiate an aberrant T cell response. After interaction with dendritic cells, CD4-positive T cells with a Th1 phenotype release cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α, which induce differentiation and increased function of macrophages, and also induce the coalescence of multinucleated giant cells, thus promoting the formation of granuloma. T cells with an induced Th17 phenotype release IL-17, which attracts and activates neutrophils in the vessel wall. Macrophages release IL-1 and IL-6, matrix metalloproteinase, and reactive oxygen species (which induce oxidative injury and degradation of media and intima layers, and disruption of the elastic laminae), vascular endothelial growth factor (leading to neoangiogenesis), fibroblast growth factor, and platelet-derived growth factor, which result in exuberant intimal proliferation. IFN-γ, TNF-α, IL-6, IL-8, IL-17A, and IL-18 likely play a role in vessel wall damage (through the recruitment of mononuclear cells in the vessel wall) and systemic features of TA. CD8-positive T cells, γδ T-cells, and natural killer (NK) cells release of perforin and granzyme-B, which contribute to apoptosis and necrosis of smooth muscle cells and damage in the intimate layer. AAECA may also have a role in the pathogenesis through the activation of endothelial cells and induction of complement- and cell-mediated cytotoxicity. Degenerative changes in the media and adventitia, as well as intimal fibrocellular hyperplasia, eventually lead to muscular layer weakening, aneurismal formation, vascular stenosis and thrombus formation [4].

PATHOLOGY

The early stages show an inflammatory infiltrate of plasma cells and lymphocytes, predominantly in the adventicia and outer layer of the intima. The process progresses to involve the entire media with neovascularization, diffuse inflammation, and occasional giant cells. The inflammatory process ultimately gives way to fibrosis beginning in the adventitia and extending into the media. Coexistent intimal proliferation is often extensive and may obliterate the lumen [9]. Aneurysm is formed when the inflammatory process proceeds quicker than the formation of a sufficient amount of connective tissue [6].

There are four types of vascular lesions:

1. Stenosis – most commonly affects the thoracic aorta and renal region of abdominal aorta
2. Occlusion – affects the distal part of abdominal aorta and the bifurcation zone
3. Dilation – predominantly spreads in the ascending aorta
4. Aneurysm – spreads in the lower part of thoracic aorta and abdominal aorta [6].

Alternating lesions of stenosis and dilatation with intervening normal aorta are specific features of TA. Dilation or aneurysm formation at spots of previous stenosis is a late complication [8].

The affected arteries are most often: left subclavian artery (53-90%), right subclavian artery (38-57%), left common carotid artery (30-59%), right common carotid artery (15-40%), left vertebral artery (11-48%), left renal artery (23-44%), right renal artery (33-38%), right vertebral artery (4-21%) [6].

ANGIOGRAPHIC CLASSIFICATION

The 1994 International TA Conference in Tokyo established an angiographic classification on the basis of the distribution of the lesions. Takayasu arteritis can be divided into the following five types (Fig. 1) [4, 5, 6, 8].

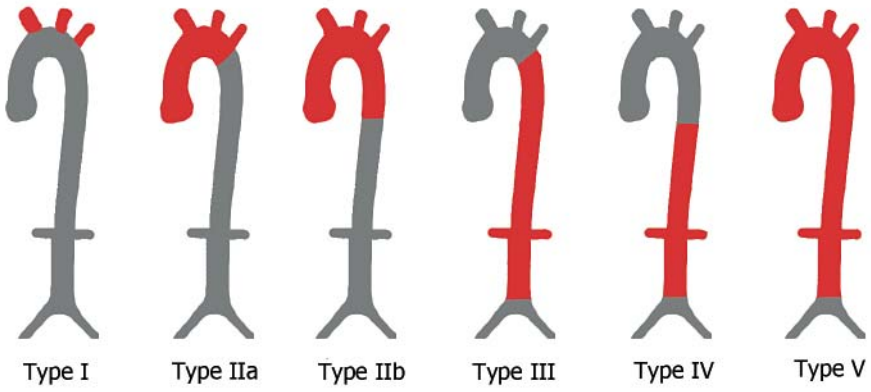


Fig. 1. Angiographic classification of Takayasu's arteritis

CLINICAL MANIFESTATIONS

First stage – general manifestations

General features are most frequent at disease onset and include: headaches (31%), fever (29%), dyspnoea (23%), weight loss (22%), vomiting (20%), and musculoskeletal features (myalgia, arthralgia or arthritis) (14%). This initial phase may last for several months or even years (4). The diagnosis might be difficult because of the nonspecific symptoms at this stage [6].

Second stage – organ-specific manifestations

Cardiovascular features: cardiovascular features have been observed in 70% of patients. They are: cardiomegaly (70%), left ventricular hypertrophy (41%), heart failure (28%), angina caused by coronary stenosis (14%) (Fig. 2A, Fig. 2B), mitral regurgitation (14%), conduction system disorders (12%), aortic regurgitation caused by aortic annulus dilatation (11%), right ventricular hypertrophy (9%) [6].

The most common cardiovascular findings are bruits, which are present in over 90% of patients. The typical locations for these bruits are over the carotid arteries and abdominal aorta. Pulse deficits are usually found in the upper extremities (Fig. 3A, Fig. 3B). These do not well correlate with symptoms of claudication, as the gradual pace of obstruction frequently allows for the development of collateral circulation (Fig. 4A, Fig. 4B) [4].

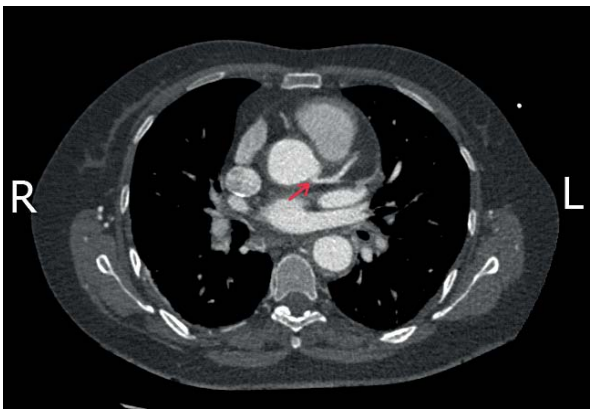


Fig. 2A. CT scan of the aortic root (axial plane). Suspect of left main coronary artery ostial stenosis (red arrow)

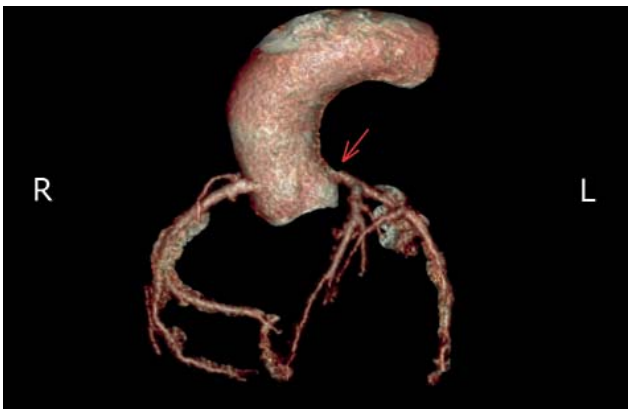


Fig. 2B. 3D reconstruction obtained from the CT scan of aorta and coronary arteries. Suspect of left main coronary artery ostial stenosis (red arrow)

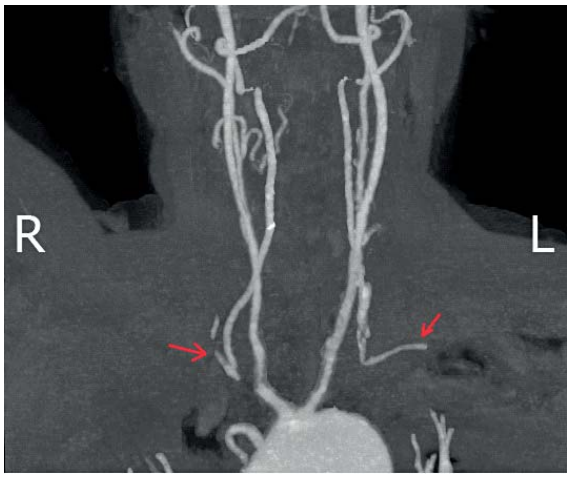


Fig. 3A. CT scan of aortic arch and its branches (frontal plane). Bilateral severe subclavian artery stenosis (red arrows)

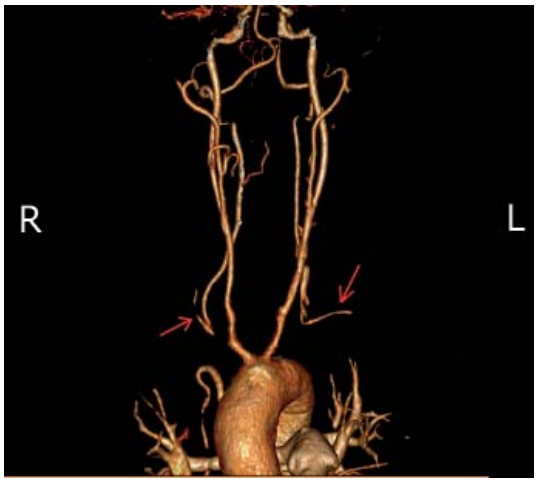


Fig. 3B. 3D reconstruction obtained from the CT scan of aortic arch and its branches. Bilateral severe subclavian artery stenosis (red arrows)

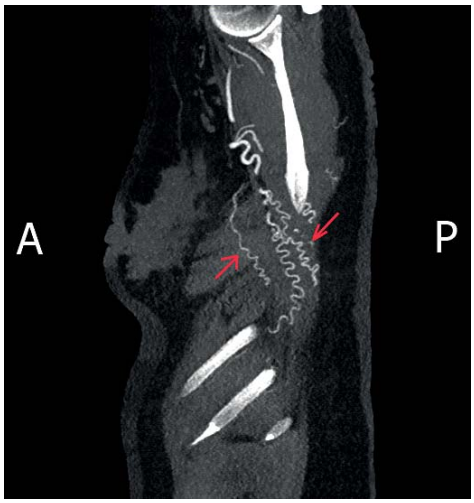


Fig. 4A. CT scan of thorax (sagittal plane). Collateral vessels provide an alternative source of blood supply to the upper extremities (red arrows)

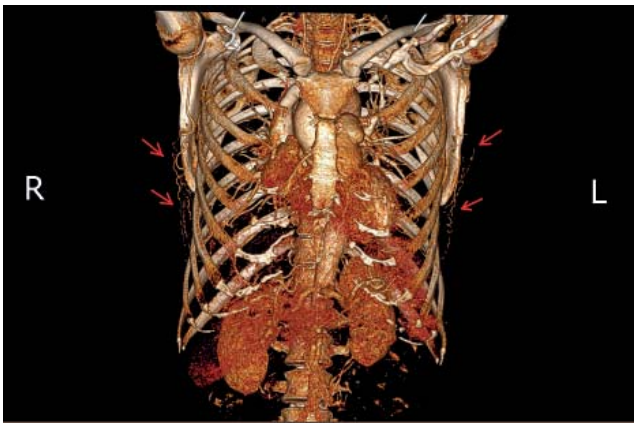


Fig. 4B. 3D reconstruction obtained from the CT scan. Collateral vessels provide an alternative source of blood supply to the upper extremities (red arrows)

Hypertension (found in 50% of the patients) is based on renal vascular stenosis and/or reduction of the baroreceptor response. The blood pressure is higher in the upper extremities than lower ones. The arterial hypertension deteriorates the prognosis and the course of the disease. The 10-year survival rate is 15% lower in patients with high blood pressure [6].

Extremities features: claudication, paresthesia, cyanosis [4].

Carotidynia (pain and tenderness on palpation over carotid bifurcation) is one of the most distinctive symptoms during the acute phases of the disease. Carotidynia may be aggravated by swallowing, coughing, sneezing or turning the head to the contralateral side [4].

Kidney features are delivered in three ways:

1. Ischaemic nephropathy – the renal artery stenosis occurs in the III, IV and V types of TA and can lead to renovascular hypertension. The frequency is unknown. Ostial stenosis is most common, but we must consider the possibility of bilateral involvement (Fig. 5). Ischemia leads to diffuse atrophic processes in the glomerulus and tubules, fibrosis and focal inflammatory infiltration in the kidney.
2. Glomerulonephritis and glomerulopathy – this pathology is rare; its onset shows an activity of the immune process and vascular inflammation. The most common one is the case of mesangial proliferative glomerulonephritis and less often Ig A nephropathy, membranoproliferative glomerulonephritis and membranous glomerulonephritis.
3. Amyloidosis – secondary AA-amyloidosis is developing. Nephrotic syndrome characterizes this form of renal impairment. The life expectancy after the diagnosis of AA kidney amyloidosis and haemodialysis sessions varies from 30 to 60 months [6].

Neurological features: The most common neurological symptoms are severe headaches, organic confusion, cognitive dysfunction, stroke. Intracranial aneurysms have been reported, the middle cerebral artery is the most frequent site of involvement [4].

Gastrointestinal features: Stenotic arterial segments can cause ischemic symptoms: most frequently, acute or chronic abdominal pain is usually secondary to mesenteric ischemia caused by vasospasm of the damaged intestinal vasculature, which determines reduced blood flow in the intestine during eating (Fig. 6). Abdominal pain can be associated with vomiting or nausea, blood in the stools and diarrhoea [4].

Ocular features: Visual symptoms can be either transient or persistent and progressive. The ocular manifestations in TA usually follow the occlusion or severe stenosis of the carotid arteries, and they commonly appear late during the disease course. Signs of conjunctival and episcleral vascular dilation may occur, but retinal abnormalities are most prominent. Complications due to ischemia, vitreous haemorrhage, retinal detachment, or optic atrophy may lead to blindness. The most common retinal findings include tortuosity and dilation of retinal veins, arterio-venous shunts, and microaneurysms in the peripheral retina. Acute loss of vision, sometimes associated with orbital pain, has been reported. Vision loss may be secondary to anterior uveitis, cystoid maculopathy, or ischemic optic neuropathy [4].

Pulmonary features: Vessels in the right lung are predominantly involved (Fig. 7). Pulmonary hypertension develops frequently and may be due to pulmonary artery stenosis, left ventricular failure, or both. Patients may exhibit cough and dyspnoea, pleural effusion, pulmonary infiltrates, alveolar haemorrhage, respiratory failure [4].

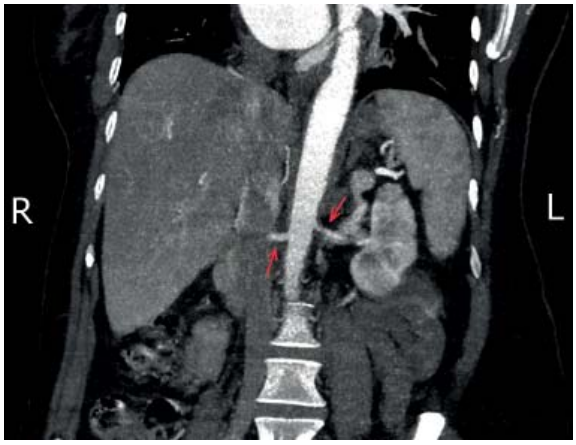


Fig. 5. CT scan of the abdominal aorta (frontal plane). Renal artery ostial stenoses (red arrows), strongly displayed on the left

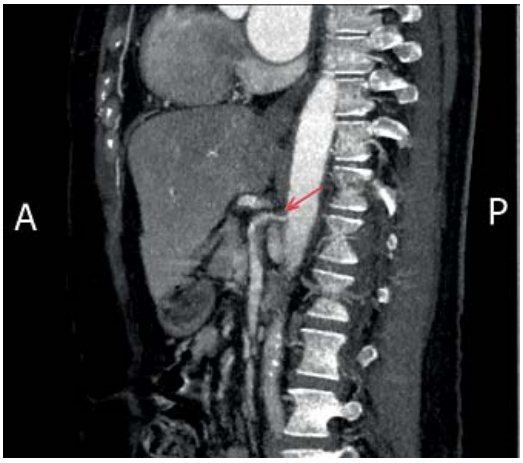


Fig. 6. CT scan of the abdominal aorta (sagittal plane). Ostial stenosis of the superior mesenteric artery (red arrow)

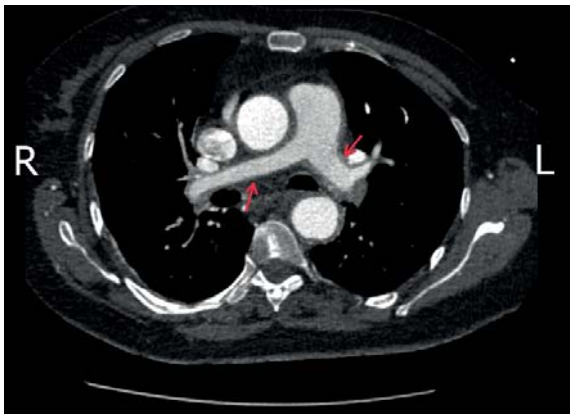


Fig. 7A. CT scan of the pulmonary trunk and large proximal branches (axial plane). Wall thickening of the pulmonary arteries (5 mm) owing to inflammation. Narrowing of the left and right pulmonary arteries, 12 mm and 10 mm respectively (red arrows)

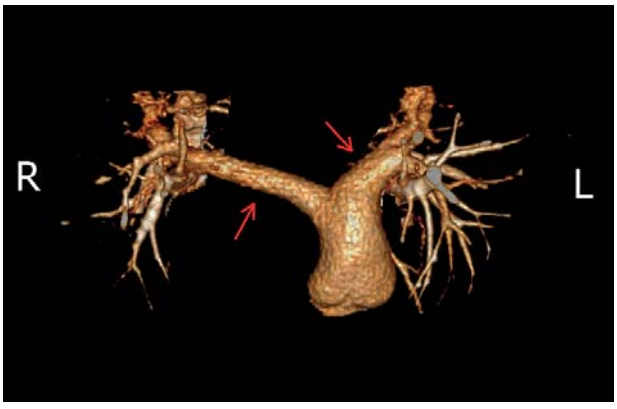


Fig. 7B. 3D reconstruction obtained from the CT scan of the pulmonary trunk and large proximal branches. Narrowing of the left and right pulmonary arteries, 12 mm and 10 mm respectively (red arrows)

Laboratory and biomarkers

There are no specific laboratory tests or available validated biomarkers of disease activity which could be useful for diagnosing the TA. Acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are the most valuable non-imaging tests used to monitor the disease course. Anemia, leukocytosis, thrombocytosis, elevated serum amyloid A and fibrinogen may also accompany active phases of the disease. Serum autoantibodies such as AECA, circulating endothelial cells, and serum proteins such as vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), IL-6 and IL-18 have been investigated as potential biomarkers for disease activity in TA, but results have been inconclusive so far. Pentraxin 3 (PTX-3) serum levels have been reported to be associated with active disease. Patients with TA had higher levels of platelet P-selectin and plasma thromboxane B2, and lower plasma cyclic adenosine monophosphate levels than healthy subjects, which indicated increased platelet activity [4].

Imaging

Imaging tests are a crucial part of diagnosing and monitoring of TA [4, 6]. Their types, advantages and disadvantages are shown in Table 2.

Diagnostic criteria

Until 1988 no diagnostic or classification criteria were available for TA, when Ishikawa proposed a set of diagnostic criteria. Ishikawa's criteria were based on the age of onset of signs and symptoms of TA, clinical, laboratory and angiographic parameters and comprised an obligatory criterion, two major criteria and nine minor criteria. In addition to the presence of the obligatory criterion, the following combinations led to a high probability of TA: two major criteria or one major criterion and two or more minor criteria or four or

Table 2. Imaging modalities in the evaluation of Takayasu arteritis patients

Types	Advantages	Disadvantages
X-ray	Viewed: calcification of the aorta, dilatation of the ascending aorta, cardiomegaly	Radiation
Doppler ultrasound	Very good measurement of arterial wall thickness Provides fair definition of anatomical details Fair sensitivity for assessment of disease activity Non-invasive Inexpensive No radiation	Operator-dependant Poor definition of descending aorta
Digital substraction angiography	Excellent morphological definition Allows vision of distal vessels	Radiation Invasive Low sensitivity for assessment of disease activity Does not provide information about vessel wall
Magnetic resonance angiography	Good morphological definition Fairly good measurement of arterial wall thickness Allows vision of arterial wall edema Provides information on gadolinium uptake in vessel wall Good sensitivity for assessment of inflammation No radiation	Does not allows vision of small vessels It may overestimate stenosis Expensive
Computed tomography angiography	Good morphological definition Fairly good measurement of arterial wall thickness Good imaging of arterial lumen	Low sensitivity for assessment of disease activity Does not allows vision of small vessels Radiation
18F-fluoro-deoxy-glucose positron emission tomography	Good sensitivity for early assessment of inflammation	Radiation Expensive Very poor definition of anatomic details

more minor criteria (Table 3). The main criticism on the Ishikawa's diagnostic criteria for TA includes the age restriction for the disease onset (< 40 years). Modifications on Ishikawa's diagnostic criteria for TA were suggested in 1995 by Sharma et al., and included the removal of the obligatory criterion (age < 40 years). A high probability of TA is considered when two major criteria are present or one major and two minor criteria or four minor criteria are present (Table 4) [10].

Table 3. Ishikawa diagnostic criteria for Takayasu arteritis

Obligatory criterion:
Age < 40 years
Major criteria
1. Left mid subclavian artery lesion
2. Right mid subclavian artery lesion
Minor criteria
1. High ESR
2. Carotid artery tenderness
3. Hypertension
4. Aortic regurgitation or Annuloaortic ectasia
5. Pulmonary artery lesion
6. Left mid common carotid lesion
7. Distal brachiocephalic trunk lesion
8. Descending thoracic aorta lesion
9. Abdominal aorta lesion

Table 4. Ishikawa's diagnostic criteria for TA modified by Sharma et al.

Major criteria
1. Left mid subclavian artery lesion
2. Right mid subclavian artery lesion
3. Characteristic signs and symptoms of at least one month duration
Minor criteria
1. High ESR
2. Carotid artery tenderness
3. Hypertension
4. Aortic regurgitation or annuloaortic ectasia
5. Pulmonary artery lesion
6. Left mid common carotid lesion
7. Distal brachiocephalic trunk lesion
8. Descending thoracic aorta lesion
9. Abdominal aorta lesion
10. Coronary artery lesion

Management

Treatment of TA is directed at controlling vascular inflammation and preventing irreversible organ damage.

1. Non-medical treatment – quitting smoking is related to reduction of the vasospastic reaction [6].
2. Medical treatment – The management of large-vessel vasculitis can include early initiation of corticosteroid therapy for induction of remission, use of immunosuppressive agents as adjunctive therapy and clinical monitoring of therapy with inflammatory markers as supportive data [4].

The treatment begins with corticosteroids at a dose of (Cs) 0.5-1 mg/kg (up to 60 mg/per day) per month. If the symptoms persist after this period or if it is impossible to reduce the dose within three months, immunosuppressant (IS) – azathioprine, methotrexate, mycophenolatemofetil, leflunomide or cyclophosphamide – should be added [6]. The IS treatment continues one year after the remission. Simultaneously the dose of CS is gradually decreased until its complete stop [4]. If recurrent symptoms appear, the CS have to be taken at the same dosage as before [6].

In patients who are refractory to other therapies biological treatment can be used – TNF-inhibitors (etanercept), anti-TNF-α monoclonal antibodies (adalimumab, infliximab), the IL-6 inhibitor (tocilizumab) and B-cell-directed strategies such as the monoclonal anti-CD20 antibody (rituximab) [4, 6]. The initial dose and mode of administration could vary due to the severity of the disease and the difference in drug actions. To avoid undesirable effects, a minimal effective dose must be used [6].

Arterial hypertension

General measures include blood pressure control: beta-adrenergic blockers, calcium channel blockers, diuretics or angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors should be carefully used in patients with renal artery stenosis [4]. It shouldn't be forgotten that the reduction in blood pressure in cases of significant stenosis of the carotid and spinal-cerebral arteries creates a risk for neurological complications [6].

Additionally, since patients with TA may have a hypercoagulable state, some authors advocate the use of heparin or anti-platelet therapy in order to reduce the incidence of ischemic events [4].

Endovascular procedures and surgical treatment

Percutaneous transluminal angioplasty is used in stenotic areas. Surgery has a relevant adjunctive role in the management of patients with TA. The methods of surgical treatment are endarterectomy, bypass procedures, resection of coarctation and aneurysm regions, and aortic valve replacement [11].

Prognosis

The development of the disease is often unpredictable. For a period of months and years the pro-

gression is slow [11]. The 5-year and 10-year survival rates are 93% and 91% respectively. In the absence of treatment, the 10-year survival rate is less than 70% [6].

CONCLUSION

Takayasu arteritis is an idiopathic granulomatous vasculitis of the aorta and its main branches. It frequently occurs in young or middle – aged women of Asian origin, yet anyone can be affected. There should be inflammation and intimal proliferation leading to wall thickening, stenotic or occlusive lesions, and thrombosis, while destruction of the elastic and muscularis layers cause aneurysms. The etiology is unknown – a genetic predisposition to the disease is presumed, autoimmune etiology is also possible. There is evidence of an association between Takayasu's arteritis and HLA subtypes. Early diagnosis and treatment are important for reducing morbidity and mortality. Treatment of TA is focused on controlling vascular inflammation and preventing irreversible organ damage. The therapy with CS and IS are the main treatment choices. In case of refractory cases biological agents should be used as soon as possible to prevent organ damage due to ischemia. Revascularization is preferred during severe arterial stenosis using endovascular (percutaneous transluminal angioplasty) or bypass interventions.

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