TAKAYASU’S ARTERITIS – AN UPDATE

Daniela Bartoș¹, Ecaterina Bontaș¹, S. Ghiorghe¹

Abstract: Takayasu’s arteritis (TA) is a chronic large vessel vasculitis. The pathology of TA has not been totally revealed, but it seems to be mainly secondary to cellular immunity. Commonly, it occurs in female patients under 40 years of age and usually involves the aorta and its large branches. Disease may be heterogeneous in manifestation and is characterized by frequent relapses. General symptoms frequently consist of severe fatigue, low-grade fever, and weight loss. Signs and symptoms might be non-specific and usual blood tests inaccurate. Diagnosis is based on symptoms, physical findings, and imaging, because histological exam is rarely useful. The current “gold standard” investigation, the angiography, is invasive and identifies in an advanced stage the structural changes of vessels. Glucocorticoids and cytotoxic drugs, as well as usual follow up and surgical intervention in many cases represent the conventional treatment.

Key Words: Takayasu’arteritis, vasculitis, connective tissue diseases.

1 - Department of Internal Medicine and Cardiology, Emergency Hospital Floreasca Bucharest.

Background

The systemic vasculitides are heterogeneous conditions of unknown etiology characterized by inflammation and necrosis of various sizes of blood vessels. The incidence of vasculitis is inconsistent and most cases are diagnosed in the fifth decade of life. Currently, there are two common classifications published by the American College of Rheumatology and Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis. Excepting cutaneous leukocytoclastic angiitis, vasculitides in these classifications are systemic disorders affecting more than one organ.

Classification of vasculitides Chapel-Hill Conference, 1994 is based on clinical and histopathologic features, the size of the predominant vessel involved, the presence of serological markers and other immune phenomena, and the affected tissue, as demonstrated by immunohistochemistry. Currently, the Classification of vasculitides Chapel-Hill Conference, 1994 is based on the presence of circulating anti-neutrophil cytoplasmic antibodies (ANCA) (Fig.1). ANCA are specific for antigens in granules in neutrophils (and monocytes) detected by indirect immunofluorescence microscopy or immunochemical tests. ANCA have two positive test patterns: diffuse cytoplasmic (“C-ANCA”) and perinuclear only (“P-ANCA”). C-ANCA are in 90% - antibodies against antiprotease-3 associated with Wegener’s granulomatosis; and P-ANCA are in 90% - antibodies against myeloperoxidase associated with microscopic polyangiitis and Churg-Strauss syndrome. In the presence of cytokines, myeloperoxidase and proteinase 3 are expressed on cell surface, and binding of ANCA to these cells causes them to become activated, degranulate, and release inflammatory mediators. Vessel walls in the area become inflamed.

On the other hand, there are diseases that mimic vasculitis: infective endocarditis, Streptococcal infections, atrial myxomas, amyloidosis, cholesterol emboli, and drug abuse. The pathogenesis of most forms of vasculitis is unclear but comprises immune complex deposition, humoral immune responses, T-cell mediated immunity, autoantibodies, and cytokine activation mechanisms. The clinical red flags (Fig.2) for vasculitides are unexplained hemoptysis, palpable purpura or petechiae, fever of unknown origin, livedo...
reticularis, eosinophilia, bowel ischemia and infarction, glomerulonephritis, mononeuritis multiplex, and unexplained stroke. ANCA are pathogenic, are useful in diagnosis of vasculitis, and may fluctuate with disease activity. It is unusual for a vasculitic process to affect only one organ system. In most cases, it is essential to biopsy tissue in order to make a diagnosis. Diagnosis of vasculites is based on clinical picture, serology, and pattern of renal disease that generally requires biopsy. Renal pathology may be fitting but not specific, and usually with typical focal necrotizing glomeronephritis, with or without immune deposits.

**Definition and epidemiologic data of TA**

Takayasu’s arteritis (TA) is an uncommon chronic granulomatous necrotizing vasculitis that involves large and medium sized arteries, mainly the thoracoabdominal aorta, its branches and pulmonary arteries.

The discovery of Takayasu’s arteritis can be traced back in 1830, when the Japanese Rokushu Yamamoto reported on it. Also known by the terms “pulseless disease”, “occlusive thromboaortopathy”, and “Martorell syndrome”, this vascular disorder was scientifically described for the first time in 1908 by Mikito Takayasu, a Japanese ophthalmologist, at the 12th Annual Meeting of the Japan Ophthalmology Society. His case was a 21-year-old Japanese girl with retinal neovascularization and absent upper-extremity pulses. Later in 1990, this type of aortoarteritis was defined and classified by the American College of Rheumatology as “Takayasu’s arteritis is an idiopathic inflammatory disease of the large elastic arteries occurring in the young and resulting in occlusive or ectatic changes mainly in the aorta and its immediate branches as well as the pulmonary artery and its branches.”

Takayasu’s arteritis may be diagnosed from childhood to late adult life, and it rarely occurs over 40 years of age. This condition is not common, however is progressive, and the prognosis is poor. Takayasu’s arteritis has a relatively uniform global incidence of 1-2/million. Females make up 80%-90% of patients with Takayasu arteritis, mostly in the second and third decades of life. Men are rarely affected. It is more frequent in the Orient, mainly in Asia, but it may also occur in North America, Europa, Africa, and Middle East.

**Pathophysiology**

The cause of TA is not known, but the order of pathophysiologic modifications includes arterial media destruction, with aneurysm progress and, rarely with fissuring arteries. Histopathologically, TA changes include an adventitial mononuclear infiltrate with perivascular cuffing of the vasa vasorum, followed by medullary mononuclear inflammation, and rarely is associated with granulomatous modifications. The subclavian artery, common carotid artery, vertebral artery, and renal artery are more often affected.

**Diagnosis criteria**

Delay in diagnosis of TA is very common. In addition, a chronic, relapsing course is common. The diagnosis of TA is largely based on the combination of 1) clinical manifestations, 2) laboratory evaluation, and 3) diagnostic imaging. When the diagnosis is presumed, it is typically confirmed by a radiographic technique. Diagnosis is based on symptoms, physical findings, and imaging, because tissue diagnosis is rarely feasible.

The patient must meet 3 out of the following 6 criteria of American College Rheumatology Classification Criteria to be diagnosed with Takayasu’s arteritis:

- age under 40 at disease onset;
- claudication of extremities;
- decreased branchial artery pulse;
- blood pressure difference >10 mmHg between arms;
- bruit over subclavian arteries or aorta;
- Arteriogram abnormality: occlusion or narrowing in aorta or main branches.

**Clinical Presentation**

Symptoms consist of aphasia, transient hemiparesis, unilateral transient amblyopia or persistent blindness, headache, vertigo, syncopal attacks, and muscle wasting. Symptoms of vascular compromise can be minimized by the development of collateral circulation when there is a gradual progress of stenosis. Bruits and diminished or absent pulses are the most constant signs. This disease seems to have two different stages, an early stage that is characterized by an inflammatory process, and a later stage characterized by vascular occlusion. The clinical presentation of TA includes the following phases:

- the early phase or prepulseless phase described by nonspecific systemic features (malaise, arthralgia, mild synovitis, weakness, myalgias weight loss, and low-grade fever),
- the pulseless phase (vascular inflammatory phase) is characterized by claudication, headaches, dizziness, and amaurosis or diplopia, difficulty in
looking upwards, renovascular hypertension, chest pain or palpitation, pulmonary (dyspnea, hemoptysis and pleurisy), gastrointestinal (anorexia, nausea), and skin (rare, eritem modosum, ulcers).

- **the occlusive phase**: usually involves common carotid artery (visual defects, strokes, TIA), vertebral artery (dizziness, visual defects), subclavian artery (arm claudication), aorta (aortic regurgitation, cardiac heart failure), pulmonary artery, cardiac and celiac axis, renal artery ( renovascular hypertension), iliac artery (claudication).

The occlusive fibrotic phase is dominated by ischemic symptoms including angina, claudication, syncope, and visual impairment⁶, hypertension from renal artery stenosis, aortic regurgitation from aortitis, or stroke from carotid artery occlusion. Late-phase TA may be subclassified as classic pulseless disease (type 1), a mixed type (type 2), an atypical coarctation type (type 3), and a dilated type (type 4)¹⁰. The most cases are diagnosed in the form of late-phase disease⁶. As an aid to establishing the clinical diagnosis, several criteria have been proposed. The Ishikawa diagnostic criteria modified by Sharma et al¹⁴ (1995) are currently the most commonly adopted:

- **Type I** involves only the branches of the aortic arch.
- **Type IIa** involves the aorta only at its ascending portion and/or at the aortic arch. The branches of the aortic arch may be involved as well. The rest of the aorta is not affected.
- **Type IIb** affects the descending thoracic aorta with or without involvement of the ascending aorta or the aortic arch with its branches. The abdominal aorta is not involved.
- **Type III** is concomitant involvement of the descending thoracic aorta, the abdominal aorta, and/or the renal arteries. The ascending aorta, the aortic arch, and its branches are not involved.
- **Type IV** involves only the abdominal aorta and/or the renal arteries.
- **Type V** is a generalized type, with combined features of the other types.

**Laboratory findings**

There is no specific lab test⁶,¹⁵. In the case of “disease activity,” it may be detected an elevated erythrocyte sedimentation rate (ESR), raised C-reactive protein, and anemia.

**Imaging Findings**

The investigation of choice for the diagnostic evaluation of TA¹⁶,¹⁷ is angiography - conventional or digital subtraction that can show long, smooth, tapered stenoses with collateral developed circulation¹⁸.

Echocardiography and Duplex Doppler ultrasonography are the first investigations and the characteristic findings of TA consist of wall thickening, stenosis, aneurysms, calcifications, occlusions, and pulsatility. Computed tomography (CT) and magnetic resonance imaging (MRI) are the best diagnostic techniques for assessing pulmonary vascular lesions. In Takayasu’s arteritis the pulmonary arteries are less frequently involved than the aorta. The usual findings of CT angiography include concentric arterial wall thickening affecting the vessels (mainly aorta and its branches, the pulmonary arteries, and occasionally the coronary arteries), aneurysms, stenoses, and occlusions⁵,¹⁰,¹⁶-²⁰. The MRI can show mural thrombi, fusiform vascular dilation, thickened aortic valvular cusps, multifocal stenoses, signal alterations within and adjacent inflamed vessels, and concentric thickening of the aortic wall¹⁰,¹⁸, and ²⁰.

Currently, the PET (positron emission tomography) technique or [(18) F] FDG-PET (118 F-fluorodeoxyglucose positron emission tomography) is highly effective in evaluating the activity degree and the level of large-vessel vasculitis ²¹ in arteries with a diameter larger than 4 mm, including TA ²¹. The mechanism of PET is efficient because inflammatory cells pick up [18F] fluorodeoxyglucose [(18F) FDG]²¹. Compared to other techniques, PET permits an early diagnosis of TA²⁴ during the inflammatory or “pre-pulseless” phase²¹. Moreover, (18)FDG PET is useful for assessing the efficacy of the steroid therapy in addition to making a diagnosis of Takayasu’s arteritis associated with Hughes antiphospholipid syndrome ²²,²³.

Prognosis depends on clinical course, complications, and age of patients. Death usually occurs 20 years after onset of symptoms has been reported.

**Treatment**

High-dose corticosteroids are the mainstay of TA therapy if caught early. Initial treatment consists of prednisone 1 mg/kg/day given for the first 1–3 months, then reduction after an alternate-day plan. Cytotoxic therapy is mainly used in cases with ongoing disease activity, regardless of glucocorticoid therapy. The
combination of methotrexate 15–25 mg/week plus glucocorticoids is believed to induce remission and to reduce glucocorticoid therapy and toxicity. Cyclophosphamide is indicated for patients with active inflammatory disease and in case of the failure of glucocorticoid or methotrexate therapy. Cyclosporine is used instead of cyclophosphamide for patients that desire to preserve fertility. Treatment of symptomatic fibrotic lesions with stenoses or occlusions needs surgical therapy, mainly by angioplasty with or without stenting; and vascular resection with grafts. The indications for surgery comprise cerebral hypoperfusion, renovascular hypertension, limb claudication, repair of aneurysms, or valvular insufficiency. Percutaneous transluminal angioplasty is the best option in controlling hypertension linked to renal artery stenosis; however, the percentage of restenosis is more frequent in TA than in atherosclerotic lesions.

References: