Takayasu’s Arteritis

ABSTRACT

Takayasu’s arteritis is a chronic nonspecific arteritis due to inflammatory process of the large vessels usually affecting young women. Occlusion of aorta and its various major branches can result in many of its clinical manifestations, the most devastating being stroke. As with other noninfectious inflammatory diseases, steroid remains the mainstay of treatment with many other avenues being searched for.

Keywords: Arteritis, Diagnosis, Positron emission tomography, Vasculitis.

INTRODUCTION

Takayasu’s arteritis is a rare, systemic inflammatory large vessel vasculitis that usually affects women of the childbearing age. It is defined by the Chapel Hill Consensus conference on the nomenclature of systemic vasculitis as “granulomatous inflammation of the aorta and its major branches.”1 Also known as pulse less disease or occlusive thromboarthropathy, the disease is named after the Japanese ophthalmologist who described a form of retinal arteriovenous anastomoses caused by retinal ischemia due to large vessel vasculitis in 1905.

Epidemiology

The disease is more common in Asian population with numbers as high as 150 per million in Japan.2 The incidence is also high in India but the exact numbers are lacking. An association with the tubercle bacilli, though present, a’int much strong.3 The median age of presentation is 25 years; however, approximately 25% of cases begin before 20 years of age and 10 to 20% present after 40 years of age.4

Pathogenesis

The pathogenesis of Takayasu’s arteritis starts in a genetically predisposed individual with perhaps a specific hormonal milieu, followed by an exposure to unidentified antigen leading to mounting of an immunological response that targets large vessels.3 Macroscopically, in the chronic phase, the aorta is thickened secondary to fibrosis of all three vessel layers. The lumen is narrowed in a patchy distribution, often affecting multiple areas. If disease progression is rapid, fibrosis can be inadequate with subsequent aneurysm formation. The intima may be ridged, with a “tree bark” appearance, a feature common to many aortitides.5

Microscopically, the vasculitis may be divided into an acute florid inflammatory phase and a healed fibrotic phase. In the acute phase, a vasa vasoritis is seen in the adventitia. The media is infiltrated by lymphocytes and occasional giant cells with neovascularization. Mucopolysaccharides, smooth muscle cells, and fibroblasts thicken the intima. In the chronic phase there is fibrosis with destruction of elastic tissue. This can lead to aneurysm formation. Similar histopathological findings are also seen in giant cell arteritis; therefore, biopsy results may not differentiate between these two vasculitides.6 Infiltration with gamma–delta T-cells in aortic tissues results in damage of the layers of the vessel wall by perforin. Recognition of heat shock protein 65 may result in recognition and adhesion of these cells. They have previously found restricted VaVβ gene usage of the alpha–beta T-cell receptor, suggesting that a specific antigen was being targeted. More recently, they have reported restricted usage of the VγVδ genes in the infiltrating gamma–delta T-cells, supporting their hypothesis, along with the expression of various costimulatory molecules necessary for T-cell activation.7

Some patients also had titers of antiendothelial antibodies, which in one study was found in 18 out of 19 patients with titers 20 times greater than the normal levels.8 Antinuclear antibodies, antineutrophilic antibodies, or antiphospholipid antibodies were all negative in all patients with Takayasu arteritis. Accelerated atherosclerosis determined by carotid plaque and intimal thickness using Doppler studies showed higher prevalence in diseased population as compared to general population.9

Infection has long been thought to have a role in the pathogenesis of the disease. Tuberculosis has been particularly implicated in view of the high prevalence of infection, past or present, in affected patients10 largely...
from endemic areas. More recently, viral infection is being investigated as a trigger of vasculitis. Takayasu arteritis has been associated with different human leukocyte antigen (HLA) alleles in different populations. For example, in Japan and Korea, there is a clear association with the extended haplotype: HLA B*52, DRB1*1502, DRB5*0102, DQA1*0103, DQB1*0601, DPA1*02-DPB1*0901.12,13

CLINICAL FEATURES

The patient of Takayasu arteritis can be completely asymptomatic, the disease being discovered on routine physical examination depicting absent pulses or may present as a devastating complication like stroke. Because of the disease process involving the upper limb arteries more than the lower limb, arm claudication is usually the first symptom. Lower limb claudication usually occurs after symptoms have started in upper limb. Bruit can be heard over the stenosed arteries but they may eventually become silent when critical stenosis develops inhibiting the turbulence. Unequal blood pressure in the arms may also be seen as subclavian steal. Advanced occlusion can lead to formation of nonhealing ulcers and gangrene, but this is uncommon given the development of collateral circulation because of the chronic nature of the disease. Arthralgias and myalgias occurred in more than half of the patients. Skin involvement occurred in the form of erythema nodosum or at times, pyoderma gangrenosum. Other symptoms occur due to stenosis and resultant of the ischemic damage of the organ supplied. Involvement of the pulmonary artery is uncommon and can lead to pulmonary hypertension. Aortic root dilatation and resultant aortic regurgitation (AR) can occur. Myocardial infarction can occur due to coronary vasculitis. Myocarditis and pericarditis can occur but are rare. Abdominal pain can be due to mesenteric ischemia. Rarely though, Takayasu arteritis can present as pyrexia of unknown origin months before appearance of symptoms suggestive of stenosis. Hypertension may develop in more than 50% of the patients and may be due to involvement of the renal arteries. Since the upper limb arteries are usually severely stenosed, the blood pressures need to be taken in lower limbs.14,15

The criteria laid down by the American College of Rheumatology for classification of Takayasu arteritis had a sensitivity of 91% and specificity of 98% for the diagnosis. Three or more criteria out of six should be fulfilled for it. The criteria are: (1) Onset before 40 years of age; (2) limb claudication; (3) decreased brachial arterial pulse; (4) unequal arm blood pressure (>10 mm Hg); (5) subclavian or aortic root bruit; and (6) angiographic evidence of narrowing or occlusion of aorta or its primary branches, or large limb arteries.16

Earlier, another set of criteria was proposed by Ishikawa in 1988 for the clinical diagnosis of Takayasu’s arteritis. It was based on a study conducted on 108 Japanese patients. In addition to the presence of the obligatory criterion, the presence of 2 major, 4 minor, or 1 major plus 2 minor criteria suggests a high probability of Takayasu’s disease with 84% sensitivity. These criteria are not widely used currently.

Obligatory Criterion

Age less than or equal to 40 years

Major Criteria

- Lesion of the left mid-subclavian artery
- Lesion of the right mid-subclavian artery.

Minor Criteria

- High erythrocyte sedimentation rate (ESR)
- Common carotid artery tenderness
- Hypertension
- Aortic regurgitation or anulooaortic ectasia
- Lesions of the pulmonary artery
- Lesions of the left mid common carotid artery
- Lesions of the distal brachiocephalic trunk
- Lesions of the thoracic aorta
- Lesions of the abdominal aorta.17

CLASSIFICATION OF TAKAYASU ARTERITIS

The year 1994 saw the advent of the angiographic classification of Takayasu arteritis being added into the literature.

- Type I: Branches of the aortic arch
- Type II(a): Ascending aorta, aortic arch, and its branches
- Type II(b): Ascending aorta, aortic arch and its branches, and thoracic aorta
- Type III: Thoracic, abdominal, and/or renal arteries
- Type IV: Abdominal aorta and renal arteries
- Type V: Combined type II(b) and IV.

– Coronary and pulmonary arteries involvement can be designated as C+ or P+.18

The prognosis of the disease was explained by Ishikawa in his study from Japanese patients. He then proposed a classification which then helped to prognosticate the disease. The four most important complications were defined as Takayasu retinopathy, secondary hypertension, AR, and aneurysm formation, each being graded as mild/moderate or severe at the time of diagnosis. Four grades of disease are described.19

Group I: Uncomplicated disease, with or without pulmonary artery involvement.
Group IIA: Mild/moderate single complication together with uncomplicated disease.

Group IIB: Severe single complication together with uncomplicated disease.

Group III: Two or more complications together with uncomplicated disease.

In this study by Ishikawa, the most common cause of death was congestive heart failure or cerebrovascular accident, which was seen in groups IIB and III. All patients with AR were in group III. The 5-year survival rate in combined groups IIB and III was 70% compared with 100% in group I. The overall 5-year survival rate after diagnosis was 83.1%.

The Indian experience with this classification also gives a positive outlook toward it for quantifying the prognosis. Cumulative survival at 5 years after disease onset was 91%; after 10 years the figure was 84%, whereas event-free survival figures were 74.9 and 64% respectively. Patients with a single, mild complication or no complication at diagnosis had a 5-year event-free survival of 97% compared with 59.7% in patients with a single severe or multiple complications. No deaths occurred in patients in groups I and IIA, whereas 19.6% of patients in groups IIB and III died during follow-up, mostly from cerebrovascular disease and cardiac failure. Twenty-two major nonfatal events occurred during follow-up, with 20 of 22 occurring in groups IIB and III.10

LABORATORY INVESTIGATIONS

They are nonspecific and depict the inflammatory nature of the disease. Normocytic normochromic anemia is common due to cytokines causing anemia of chronic disease. Erythrocyte sedimentation rate and C-reactive protein (CRP) are elevated in active disease but not in all patients, ESR being more sensitive than CRP in detecting active disease.20 Pentraxin-3 (PTX3) is a recently detected acute phase reactant which has a better sensitivity for detection of active disease than ESR or CRP.21

Imaging studies are responsible for the diagnosis of this vasculopathy. Noninvasive techniques like computed tomography (CT) and magnetic resonance imaging (MRI) are almost as sensitive as conventional angiography in detecting stenosis and mural wall changes, although the conventional method still is the gold standard. Transthoracic ultrasonography assesses the ascending aorta and transesophageal route can assess the descending aorta. These techniques can be applied when the other noninvasive techniques that are contra-indicated. Histological diagnosis is usually impractical, and histological assessment is limited to those cases undergoing revascularization procedures.

Positron emission tomography (PET) can detect areas of increased uptake in the arterial walls and preliminary results suggested it to be more sensitive and lesser than or equal to MRI in detecting arterial inflammation. Its role in identifying active lesions in patients on steroid therapy is also under investigation.

DIFFERENTIAL DIAGNOSIS

Giant cell arteritis: If the same disease process of large vessel vasculitis but Michel et al23 suggested that giant cell arteritis and Takayasu arteritis can be differentiated on clinical grounds. They found that the onset of disease at the age of 40 years was the single-most discriminatory factor. Excluding age from the analysis, ethnic background and clinical signs of upper limb vascular insufficiency, shoulder stiffness, and scalp tenderness were variables that led to correct diagnoses in 95% of patients.

Tuberculosis: Tuberculosis aortitis usually affects the descending aorta. It has been speculated that Mycobacterium tuberculosis can be the triggering factor through its production of super antigens, the suggested role of which is thought to be via the stimulation of autoreactive T-cells that induce vascular damage. Studies have shown a link between M. tuberculosis and human heat shock protein and its increased expression in vessel wall with activation of T-cells that may crossreact with the same24 but other studies refute the association between the two.3

Syphilis: Tertiary stage of the disease may involve aorta and thus the age group is usually in the 5th or 6th decade. This disease is now but used to affect the ascending aorta and lead to severe aortic root dilatation and resultant regurgitation.

Other disease processes affecting large vessels are lupus, Behcet’s, rheumatoid arthritis, spondyloarthopathies, Cogan’s syndrome, and Buerger’s disease, but they all have other specific features to distinguish them from Takayasu’s.

Ergot poisoning: Can lead to critical limb ischemia due to intense vasospasm.

Fibromuscular dysplasia: It usually involves the smaller arteries and is without constitutional features. Hereditary connective tissue disorders that can affect the aortic root like Marfan and Ehlers-Danlos syndrome.

TREATMENT

Prednisone is the cornerstone of treatment of the disease in its active form. Criteria to diagnose the active stage include new onset or worsening of two or more of the following:

1. Fever or other systemic features (in the absence of other cause).
2. Elevated ESR.
3. Symptoms or signs of vascular ischemia or inflammation (e.g., claudication, absent pulse).
4. Typical angiographic lesions.²⁴

Prednisone (0.5–1 mg/kg/day) must be given for at least 8 to 12 weeks, followed by a gradual taper, not more than 10% of the original dose per week when remission occurs. Assessment of remission can be done by observing the decrease in acute phase reactants. The Indian Takayasu Clinical Activity score (ITAS2010) and a composite ITAS-A, which includes ESR and CRP, have been validated in over 300 patients and a quantitative score of clinical disease activity for patients monitoring has been provided.²⁵ If exacerbations occur, then the dose of steroid should be increased. Steroids work in approximately 50% of patients. Side effects of steroids may add on to the morbidity of the patient. Hence, steroid-sparing agents need to be added once these side effects appear or the disease does not respond. Weekly oral methotrexate (started at 0.3 mg/kg per week, with the initial dose not to exceed 15 mg/week) is a moderately effective corticosteroid-sparing drug.²⁶ Methotrexate can be gradually increased to 25 mg/week. The emphasis is on lowering the corticosteroid dose because methotrexate seldom allows the elimination of prednisone completely; most patients continue to require at least 5 to 10 mg/day of prednisone.

Leflunomide has been used in relapsed or refractory Takayasu’s arteritis and was found to be effective in a small trial.²⁷ Azathioprine in doses of 2 mg/kg is well tolerated and prevents development of new angiographic lesions, as depicted in a study done in India.²⁸ Mycophenolate mofetil as steroid-sparing agent is promising, with two trials showing good efficacy and better steroid-sparing nature.²⁹,³⁰ Its lesser side-effect profile, when compared to other immunosuppressive agents, is fascinating but further trials are required to quantify its efficacy in the disease. Small trials have shown good efficacy of antitumor necrosis factor agents, infliximab and etanercept, in treating patients with refractory Takayasu’s arteritis.³¹ Relapses occur when treatment is stopped. Tocilizumab, an interleukin-6 antagonist, has been found to be effective in refractory Takayasu.³² Cyclophosphamide, in doses of 2 mg/kg, though toxic is employed when other therapies fail.

Revascularization procedures may be attempted. Indications include hypertension with critical renal artery stenosis, extremity claudication limiting activities of daily living, cerebrovascular ischemia or critical stenoses of three or more cerebral vessels, moderate AR, and cardiac ischemia with confirmed coronary artery involvement.⁴ Percutaneous angioplasty is an available option. Bypass surgeries have a better rate of revascularization than angioplasty, and are used when the involved segment cannot be treated by angioplasty.³³,³⁴

Progressive AR may require surgical therapy either with valve replacement or with valve repair. Surgery is more difficult in this disorder since the tissue is fragile and inflamed. Mere presence of stenosis does not necessitate intervention. The gut, for example, has so rich collaterals that even critical stenoses of the celiac, superior, or inferior mesenteric arteries usually produce no symptoms and may require no surgical intervention. Moreover, many patients with arm claudication will develop collateral circulation and improve substantially over time with medical therapy alone.¹⁵

Surgical intervention should be deferred until remission; procedures done during active disease often produce disappointing results.¹⁵ Takayasu’s arteritis is a chronic disease with 20% of patients having a self-limited course.¹³ The rest have a relapsing-remitting or progressive course requiring chronic corticosteroid and/or immunosuppressive therapy. Nearly two-thirds of patients experience new angiographic lesions. Early diagnosis with a sharp clinical suspicion helps in better management of the disease.

REFERENCES


