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Co-Occurrence of Takayasu Arteritis and Tuberculosis - A Causative Dilemma.

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ABSTRACT

Takayasu arteritis is a chronic inflammatory condition causing granulomatous vasculitis of medium-sized and large arteries. It is also known as aortic arch syndrome and pulseless disease. The exact prevalence data of Takayasu arteritis in Asian countries is not available. In western world the incidence is estimated to be 2-3 per million persons/year. The pathogenesis is unknown but there is increasing association with HLA raising the possibility of immunological correlation. Most common arteries involved are aorta with its branches and pulmonary arteries. It usually affects women younger than 40 years of age. But no age is exempt and it has also been found to be affecting children in their infancy. Though the exact etiology is not known the underlying pathologic process is granulomatous inflammation with several etiologic factors having been proposed, including infection with spirochetes, Mycobacterium and streptococcal organisms. Autoimmune and genetic factors are also found to be contributing to the pathogenesis of Takayasu arteritis. It is more frequently associated in patients with human leukocyte antigen Bw52 (HLA-Bw52) and DR4 (HLA-DR4). The association of tuberculosis with Takayasu arteritis poses a significant diagnostic dilemma. Though the exact role of Mycobacterium tuberculosis in the pathogenesis of Takayasu arteritis is still unknown, patients with this disease are known to have augmented immune response to Mycobacterium tuberculosis antigens, specifically to its 65 kDa HSP. This augmented immune response suggest possible role of this organism in the immunopathogenesis of the disease. This aspect is especially relevant in Asian and African countries where tuberculosis is endemic.

Keywords: Takayasu arteritis, vasculitis, Tuberculosis, Antitubercular treatment.

INTRODUCTION

Takayasu Arteritis (TA) is a granulomatous arteritis affecting medium- sized and large arteries, primarily the aorta and its large branches as well as proximal portions of pulmonary arteries.[1] The other commonly affected arteries are coronary, renal and internal carotid arteries. Histopathological examination of the affected vessels initially may show mononuclear cell infiltrations in the adventitia and granulomas with Langerhans cells in the media, followed by disruption of the elastin layer and subsequent massive medial and intimal fibrosis.[2] These pathological changes in vessel wall may result in stenosis, occlusion, dilatation, and aneurysm formation in the affected vessels. Severe hypertension may be seen due to renal artery stenosis caused by vasculitis.[3] Cardiac involvement may be seen in the form of dilated cardiomyopathy, myocarditis, and pericarditis. Absent or diminished pulses with limb claudication and hypertension are commonly associated findings. Involvement of the carotid artery may result in ophthalmic artery hypoperfusion causing ocular ischemic syndrome and ischemia retinopathy.[4] Rarely, Takayasu arteritis has been shown to be associated with glomerulonephritis, systemic lupus erythromatosus, polymyalgia rheumatica, rheumatoid arthritis, crohn's disease and ankylosing spondylitis.[5]

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The etiology and the precise pathogenesis of Takayasu arteritis are still unknown. The pathognomonic feature is inflammatory vasculitis of medium-sized and large vessels. Several etiologic factors proposed include infection with spirochetes, mycobacterium and streptococcal organisms.[6] Autoimmune and genetic factors have also been proposed to play a role. In many patients human leukocyte antigen Bw52 (HLA-Bw52) and HLA-DR4 has been observed with increased frequency in patients with Takayasu arteritis.[7] In Western countries Takayasu arteritis is associated with HLA-

B22 in majority of the cases. CD 36d (a multifunctional membrane glycoprotein that belongs to the class B scavenger receptor family) deficiency was also demonstrated to be associated with Takayasu arteritis in many studies.[8]

Though TA is most commonly seen in Asian countries such as Japan, Korea, China, India and Singapore its incidence and prevalence data in this region is not available. The prevalence of the disease in United States is reported to be between 3-6 persons per million populations. It predominantly affects women (approximately 80% cases) in countries like Japan while this predominance tends to decrease in India where F: M ratio is found to be approximately 1.5:1.[9] The mean age is 30 years and very few cases are reported after the age of 40 years (15%).The spectrum of affection widely differs. While some patients may experience monophasic disease which is self-limiting others may get progressive or relapsing form and in such cases the treatment is quite complicated requiring immunosuppressive therapy.[10] In complicated cases the patient may get neurological complications such as stroke, seizures and focal deficits. Cardiovascular complications may include cardiomyopathy, coronary artery aneurysms, congestive cardiac failure and valvular heart diseases. Other complications may include renovascular hypertension, ischaemic retinopathy and multi-organ dysfunction. In addition to the complications caused by the disease long term use of steroids and immunosuppressants for the treatment of TA may cause posterior cataracts, hypertension, dyslipidemia, osteoporosis and avascular necrosis of femoral head.[11]

The Eular/Printo/Pres criteria of Takayasu arteritis in children require a mandatory finding of angiographic abnormalities of the aorta or its main branches and pulmonary arteries and at least one of the following five features.[12]

- Pulse deficit (lost/decreased/unequal peripheral artery pulse[s]) and/or claudication induced by activity
- Systolic blood pressure difference >10 mmHg between any limb
- Bruits or thrills over the aorta and/or its major branches
- Hypertension
- Elevated acute-phase reactant

The disease is classified based on the site of Involvement

Type 1: Aortic arch involvement
Type 2: Thoracoabdominal involvement
Type 3: Diffuse involvement
Type 4: Pulmonary Involvement
Type 5: Aneurysmal type

The association of tuberculosis with Takayasu arteritis poses a significant diagnostic dilemma. Though the exact role of Mycobacterium tuberculosis in the pathogenesis of Takayasu arteritis is still unknown patients with Takayasu arteritis are known to have augmented immune response to Mycobacterium tuberculosis antigens, specifically to its 65 kDa HSP. This augmented immune response suggest possible role of this organism in the immunopathogenesis of the disease. This aspect is especially relevant in Asian and African countries where tuberculosis is endemic.[13]

We carried out a case series of 5 patients. All patients were diagnosed to behaving Takayasu arteritis. All had a positive montoux test and received antitubercular treatment in addition to steroids and antihypertensive. The patients were followed up for a period of 6 months. This case series emphasizes the co-occurrence of tuberculosis and Takayasu arteritis especially in Asian countries where tuberculosis is endemic.

METHODOLOGY

The study was conducted in a tertiary hospital in the state of Odisha India which is highly endemic area for tuberculosis, spanning a time period of 6 months, in this study all the cases of Takayasu arteritis were included with either known or unknown associations.

RESULT

We have a series of 5 patients observed over a period of 6 months for the progression and treatment response of the disease. In our observation five cases were found to be strongly related to tuberculosis. The initial clinical presentations were varied but with one common feature of montoux positivity. Out of the studied cases 4 were females and 1 patient was male with a male to female ratio of 1:4 [Figure 1].

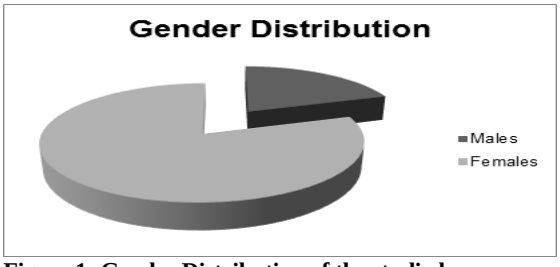

Figure 1: Gender Distribution of the studied cases.

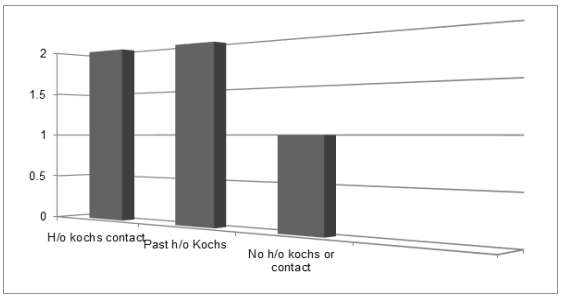

Figure 2: History of Kochs contact or past history of tuberculosis.

Table 1: Signs and symptoms present in the studied cases.

Signs and Symptoms	No of cases	Percentage
Fever	5	100%
Headache	3	60%
Vomiting	2	40%
Altered Sensorium	2	40%
Focal Deficits	1	20%
Signs of Meningitis	1	20%
Hepatomegaly	2	40%
Tachycardia	2	40%
Pedal Edema	2	40%
Papilloedema	1	20%
Blurring of Vision	2	40%

The study of signs and symptoms of the studied cases revealed that the most common sign present in the patients was fever. All patients (100%) had a history of fever and were febrile at the time of admission to the hospital. Other common features seen in the studied cases include headache (60%), vomiting (40%), altered sensorium (40%), signs of congestive heart failure (40%) and blurring of vision (40%). Least common findings were focal deficit (20%), signs of meningitis (20%) and papilloedema (20%) [Table 1]. The detail personal and family history was noted in all the patients. Clinical examination and relevant investigations were done. The History, clinical examination, investigations, diagnosis and management is summarized in Table 2. Since montoux was positive in all the patients along with either the history of contact or past history of tuberculosis in majority of the patients (80%) all patients were given AKT along with steroids. Specific treatment for hypertension, anti-failure measures and supportive management was given whenever indicated. All patients improved significantly on a 6 months follow up.

Table 2: History, clinical features, investigations, diagnosis and management in studied cases.

History	Clinical Examination	Investigations	Diagnosis and management
10-year female presented with h/o fever, altered sensorium, and weakness of right upper and lower extremities since 3 days. Family history showed that the father was an open case of tuberculosis and was on AKT for the last 5 months	No BP in Upper extremities. The strength in left Upper and lower extremity were 1/5 at presentation.	Montoux test- Positive (22mm) ESR- 35. The CT head showed infarcts over the left caudate nucleus & left tempo-parietal area. The chest CT revealed dilated pulmonary artery. Doppler of the upper limb & carotid revealed generalized concentric thickening of the bilateral common carotid artery, right brachiocephalic, left subclavian and bilateral brachial arteries with low RI in upper limb arteries	Takayasu Arteritis Type 3 Improvement in the strength with prednisone therapy. AKT (Antikochs treatment) was started due to strongly positive montoux and h/o open case of tuberculosis and raised ESR. Patient symptomatically improved at the end of follow up.
8-year-old female presented with h/o fever, headache blurring of vision and giddiness since 4-5 days No significant family history	E/o hypertension was present BP= 190/138 mm of hg. fundoscopy showed papilloedema.	Montoux - 14mm ESR-53 CRP-Positive Renal vessels doppler showed stenosis. 2D-echo-normal.	Takayasu Arteritis Type 3 Antihypertensive were given to control severe hypertension. Steroid therapy was started. AKT (Antikochs treatment) was started due to positive montoux and raised ESR. Patient symptomatically improved at the end of follow up.
7-year-old female presented with complaints of fever, breathlessness and not taking feeds properly. No significant family history. Past history revealed that the patient was treated for pulmonary tuberculosis 4 years back.	On examination there were signs of congestive cardiac failure in the form of tachycardia, pedal edema and hepatomegaly. BP= 140/98 mm of hg.	Montoux- Positive 2 D-Echo showed -hypertensive cardiomyopathy CT thorax-dilated pulmonary arteries, Doppler renal vessels & upper limb vessels showed takayasu features.	Takayasu Arteritis Type 3 Oxygen inhalation. Supportive management. Antihypertensives . Anti-failure measures. Steroids. AKT. Patient responded well and doing well on follow up at 6 months.
10-year male presented with h/o fever, headache, blurring of vision and vomiting since 3 days. Family history revealed father to be having pulmonary tuberculosis and has been on irregular treatment.	On examination patient had altered sensorium with s/o meningeal involvement in the form of positive Kernig's and Brudzinski's sign.	montoux - 16mm ESR- 42 mm CRP- Positive CSF - raised proteins. Doppler upper limb vessels showed Takayasu changes	Takayasu Arteritis Type 3 Improvement in sensorium with prednisone therapy. AKT (Antikochs treatment) was started because of positive montoux and h/o tuberculosis in the family and raised ESR. Patient symptomatically improved at the end of follow up.
14 years old female presented with h/o fever, headache and vomiting since 3-4 days. Past history revealed that patient had tuberculous pericarditis 6 months back.	On examination patient had significant hypertension BP- 180/110 mm of hg. Pedal edema, tachycardia and hepatomegaly was also present s/o congestive heart failure.	Montoux - Positive (18mm). CRP - Positive ESR - 60 CT thorax & abdomen showed dilated abdominal aorta. Renal doppler showed b/l renal artery involvement	Takayasu Arteritis Type 3 Oxygen inhalation. Supportive management. Antihypertensives . Anti-failure measures. Steroids. AKT. Patient responded well and doing well on follow up at 6 months.

DISCUSSION

The exact etiology of Takayasu arteritis is not known. A number of features suggest an autoimmune base while others raise the question that the aortitis may be an expression of tuberculin sensitization.[14] It is characterized histologically by an inflammatory cell infiltrate that affects all the layers of the arterial wall, especially the aorta and its major branches. Its incidence varies between 1.2 and 2.3 cases per million per year, and it is more common in Asians than in other racial groups. An exact epidemiological figure from our region is not available.[15]

Takayasu arteritis is a chronic vasculitis mainly involving the aorta and its main branches, such as the brachiocephalic, carotid, subclavian, vertebral and renal arteries, as well as the coronary and pulmonary arteries.[16] It induces clinically varied ischaemic symptoms due to stenotic lesions or thrombus formation, including blindness, cataract and/or retinal hemorrhage, pulselessness, aortic regurgitation and/or congestive heart failure due to dilatation of the ascending aorta. More acute progression causes destruction of the media of the arterial wall, leading to the formation of aneurysms and/or dissecting aneurysm or rupture of the involved arteries. [17]

The presentation differs in different demographic locations while Almost all patients in Japan, have ischemic disorders due to cervical lesions, presenting with dizziness, syncope, visual disturbance, faint or absent pulse, or differences in systolic blood pressure between arms in Western countries this disease usually present with absent pulses secondary to obstruction of subclavian or brachial arteries.[18]

A causal relationship between TA and tuberculosis (TB) had been suggested. Both diseases show similar pathological changes in the form of chronic inflammatory lesions and, occasionally, granulomas in the arterial walls. The genetic relationship between these two diseases has not been reported to exist until now however, both diseases have been associated with human leukocyte antigen (HLA) alleles, cold agglutinins and cryoglobulins during the acute phase of the illness.[19]

Mycobacterium tuberculosis has been implicated in the pathogenesis of Takayasu arteritis (TA). Recently, its 65 kDa heat shock protein (HSP) has been implicated in the pathogenesis of other autoimmune diseases. Patients with TA have heightened immune response to Mycobacterium tuberculosis antigens, in particular to its 65 kDa HSP, suggesting that this organism may have a role in the immunopathogenesis of this disease.[20]

The co-occurrence of Takayasu Arteritis and tuberculosis pose a dilemma for treating pediatricians or physicians since most patients eventually receive AKT along with steroids or immunosuppression the improvement cannot be attributed to any one form of this drug therapy. However it is important not to ignore the need for co-administration of AKT otherwise immunosuppression caused by steroids in these patients may cause disseminated tuberculosis. There are reports which describe the cases of complete symptomatic remission as well as the return of pulses simultaneous with anti-Tb therapy. The investigators so far have failed to isolate Mycobacterium tuberculosis in arterial lesions of either active or inactive TA but this does not necessarily exclude the possibility of a cross-reaction between mycobacterial and arterial antigens.

CONCLUSION

Takayasu arteritis is a well known yet rare form of large vessel vasculitis. This review details the history, clinical features, differential diagnoses, classification, and immunology of the disorder. Suppression of inflammation and preservation of vascular competence are the aims of treatment. The purpose of this study not only aimed at reporting a rare co-occurrence of TA with tuberculosis but also to add weightage to the causative dilemma of Takayasu Arteritis and its association with mycobacterium tuberculosis.

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