

Takayasu's arteritis: Rare but not infrequent...

**Tasnim Ahsan, Uzma Erum, Rukhshanda Jabeen, Danish Khowaja,
Urooj Lal Rehman**

ABSTRACT

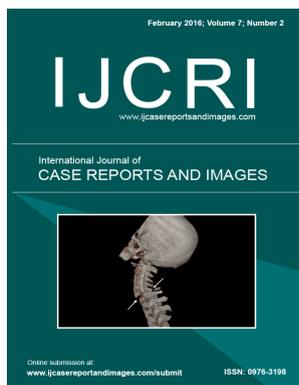
Introduction: Takayasu's arteritis is a chronic systemic vasculitis, mainly involving aorta and its major branches. It presents clinically with varied ischemic symptoms, either due to stenotic lesions or thrombus formation.

Case Series: We report a series of five patients with the diagnosis of Takayasu's arteritis. Four of them were females and one was male. The range of clinical presentation included shortness of breath leading to congestive heart failure in two patients; loss of consciousness with hemiparesis due to stroke secondary to vasculitis in one patient; limb claudication and acute severe backache in the thoracolumbar region in the other two. Two patients, the one presenting with stroke and other presenting with limb claudication, were classified as Takayasu's type-I; Two of the patients with heart failure were labeled as Takayasu's type-II and III. The patient with thoracolumbar pain was diagnosed as Takayasu's type-IV. All patients were treated with steroid and/or azathioprine.

Conclusion: Although, considered to be a rare disease, Takayasu's arteritis is not infrequent, as we report five cases seen over a four year period. A high index of suspicion is required for early diagnosis, so as to reduce the significant morbidity associated with the disease.

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disease, Takayasu's arteritis is not infrequent, as we report five cases seen over a four year period. A high index of suspicion is required for early diagnosis, so as to reduce the significant morbidity associated with the disease.

Keywords: Azathioprine, Takayasu's arteritis, Vasculitis, Immunosuppression

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INTRODUCTION

Takayasu's arteritis (TAK) is a rare, systemic, vasculitis of unknown aetiology. The disease has been reported worldwide, but it appears to be more prevalent in certain Asian countries, such as Japan, Korea, China, India, Thailand, Singapore, etc. Being a rare entity, the exact prevalence of TAK is not known. The estimated incidence of TAK in United States is reported to be 2.6 cases per million per year [1]. Although, the disease affects both genders, it appears to predominantly affect young women, especially in the second and third decade.

The aetiology of the disease is largely unknown but genetic factors, infectious triggers, autoimmune mechanisms all thought to play role in its pathogenesis. The underlying mechanism involves cell mediated inflammatory pathways, with activation of inflammatory cells such as, macrophages, cytotoxic T-cells, natural killer cells, tumor necrosis factor-alpha, and increased levels of cytokines such as interferon gamma and interleukin-6 etc. The main mediator for the inflammatory cascade

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is T-cell mediated immune response, leading to the myointimal proliferation which subsequently results in mural thickening and luminal stenosis or segmental dilatation. The disease mainly involves the aorta and its major branches. It has a heterogeneous clinical presentation depending on the site of lesion and the degree of luminal stenosis. No serological markers specific to TAK have been identified so far; angiography is considered to be the gold standard for investigation of the disease and its extent. Based on angiography, TAK is classified into six types, given in Table 1. Type III being the most common type found in South-East Asia and Africa and is called 'middle aortic syndrome'. ACR criteria is used to classify TAK, which include age, claudication of extremity, blood pressure difference in arms, presence of bruits in aorta or subclavian arteries and angiographic evidence of narrowing or occlusion of aorta or its major branches. It requires the presence of three out of six items and is 97.8% specific [2]. No single therapeutic intervention can abrogate the systemic inflammation or vascular abnormality. However, the mainstay of treatment includes immunosuppression with steroids and other immunomodulatory drugs like azathioprine, cyclosporine, etc.

CASE SERIES

We report five cases of TAK that were seen over a period of four years. All five had diverse symptoms depending upon the affected arterial territory and variably raised inflammatory markers such as ESR and CRP. The most common finding was absent or diminished upper limb pulses in four of these patients and the clinical presentation included hemiparesis due to stroke, shortness of breath secondary to congestive heart failure, limb claudication and acute severe thoracolumbar backache. A brief description of the demographic features, clinical and radiological parameters have been given in Table 2.

Case 1

A 20-year-old female presented with sudden onset right hemiparesis and loss of consciousness. Nervous system examination revealed a GCS of 10/15 (E₄M₅V₁); decreased tone on the right side and right extensor plantar response. There were absent radial, brachial and carotid pulses on both sides, while normal palpable pulses in lower limbs. Cardiovascular, chest and abdominal examinations were unremarkable. Inflammatory markers i.e., ESR and CRP were raised, 110 mm/hr and 65 mg/dl respectively, (Normal range: ESR 0-10 mm/1sthr, CRP <5 mg/L). Complete blood count (CBC), renal function and fasting lipid profile were normal. Doppler ultrasound of carotids showed completely blocked common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) on both sides with echogenic components. Aortogram showed diffuse circumferential thickening of

vascular walls involving proximal brachiocephalic, left common carotid and left subclavian artery near its origin from aorta, as well as narrowed right subclavian artery up to the axilla. Patient was diagnosed as Takayasu's type-1. Steroid with immunosuppressive agent (prednisolone plus azathioprine) were given.

Case 2

A 20-year-old male presented with progressive shortness of breath (NYHA-III) for four months, with associated orthopnea and paroxysmal nocturnal dyspnea. There was a history of left arm claudication, fatigability and malaise. He was of lean built. There were diminished pulses in left upper limb, although still palpable. Systemic examination was unremarkable. CBC, renal function and fasting lipid profile were normal. ESR and CRP were raised i.e., 45 mm/hr and 48 mg/dl respectively. Echocardiography showed severe generalized LV dysfunction with an ejection fraction (EF) of 25%. Aortogram showed mural thickening involving the ascending and descending aorta and its major branches. There was narrowing of aorta distal to the origin of left subclavian artery. This patient was labeled as Takayasu's type-III. Treated with azathioprine alone.

Case 3

A 40-year-old female presented with claudication in left arm and shortness of breath (NYHA-I) for last one month. She also had moderate intensity headache. There were feeble pulses in left upper limb with a difference of blood pressure in both arms (right arm 110/70 mmHg, left arm 90/60 mmHg). Systemic examination was unremarkable. There were raised inflammatory markers i.e., ESR 40 mm/hr and CRP 14 mg/dl. CBC, renal function, and lipid profile were normal. Echocardiography showed, normal LV with EF-58%, and enlarged right ventricle of 45 mm, with moderate tricuspid regurgitation. Aortogram showed completely occluded left common carotid artery and left subclavian artery after origin from aortic arch. Additionally, left vertebral artery originated as a separate branch from aortic arch with ostial stenosis. The patient was diagnosed as Takayasu's type-I. Treatment with high dose steroid and azathioprine was given.

Case 4

A 49-year-old female, known hypertensive for last nine years and was on calcium channel blocker (amlodipine) for hypertension control. She presented with sudden onset pain of severe intensity over the thoracolumbar region, radiating around the whole back. There was no history of fever, fatigue or limb claudication. She was afebrile, with normal blood pressure and intact pulses of both limbs and carotids. Systemic examination was also un-remarkable. Inflammatory markers were raised, i.e., ESR 90 mm/hr and CRP 10.2 mg/dl. Ultrasonography and subsequent CT angiography revealed dissecting

lesion in abdominal aorta extending up to the right renal artery. No active surgical treatment was given, as there was a delay in diagnosis and patient was stable by then. She was labeled as Takayasu’s type-IV. The patient was kept on steroid, which were gradually tapered over a period of two years and then stopped.

Case 5

18-year-old female, known asthmatic, presented with progressive shortness of breath (NYHA-II) for two months, with associated orthopnea and paroxysmal nocturnal dyspnea. There was a history of low grade fever, fatigability and malaise. There were feeble pulses in both upper limbs. Chest examination showed occasional wheezing with mild basal crackles, rest of the examination was unremarkable. CBC, renal function and fasting lipid profile were normal. ESR and CRP were mildly raised i.e., 35 mm/hr and 10 mg/dl, respectively. Echocardiography

showed severe generalized LV dysfunction with an ejection fraction (EF) of 20%. Computed tomography angiography showed circumferential thickening of aortic arch and descending thoracic aorta, with stenosis of both subclavian arteries. She was diagnosed as Takayasu’s type II, and was treated with azathioprine.

The two patients with heart failure were the youngest among the five with low BMIs. Radiological findings classified two of them as having type-I, and other three as Takayasu’s type-II, III and IV disease (Table 2). One patient was treated with steroid (prednisolone) alone, which was gradually tapered off in two years. Two patients received immunosuppression with azathioprine (AZA) alone, as they had severe heart failure; the other two were given AZA with maintenance dose steroids. These patients are being regularly followed-up; and are symptomatically improved.

Table 1: Takayasu’s arteritis types

Takayasu’s Type	Arterial Territory Involved
I	Branches of aortic arch
II-a	Ascending aorta, aortic arch and its branches
II-b	Type II-a region plus thoracic descending aorta
III	Thoracic descending aorta, abdominal aorta, renal arteries, or combination
IV	Abdominal aorta, renal arteries, or both
V	Entire aorta and its branches

Table 2: Demographic, clinical and radiographic features of patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	20	20	40	49	18
Sex	F	M	F	F	F
Mode of Presentation	Stroke	Heart Failure	Limb claudication and headache	Severe thoracolumbar pain	Heart failure
Duration of symptoms	2 days	4 months	1 month	1 day	2 months
Vascular territory involved	Brachiocephalic, Lt. Common carotid, Lt. subclavian arteries and narrowing of Rt. subclavian	Ascending and descending aorta and its major branches	Lt. common carotid and subclavian arteries	Dissecting lesion in the Abdominal aorta extending up to Rt. renal artery	Aortic arch, descending thoracic aorta, stenosis of both subclavian arteries.
Takayasu’s type	Type I	Type III	Type I	Type IV	Type II
Treatment	AZA + Prednisolone	AZA	AZA + Prednisolone	Prednisolone	AZA

Abbreviations: AZA Azathioprine, Lt left, Rt right

DISCUSSION

There is wide variation in the incidence, gender predisposition, disease morbidity and mortality reported in TAK across the globe. However, it can be concluded that some genetic or environmental pre-disposition exists in certain regions of the world, where it appears to be more common. Although considered to be idiopathic, certain mechanisms have been proposed for understanding the aetiology of the disease. The “heat-shock protein hypothesis” has been proposed, suggesting that expression of 65 kDa heat-shock protein in the aortic tissue may induce major histocompatibility class I chain-related A (MICA), located on the vascular cells hence leading to activation of inflammatory cascade [3]. Infection has also been considered as a possible trigger in the pathogenesis of TAK. Tuberculosis particularly has been implicated in endemic areas. *Mycobacterium tuberculosis* has been thought to trigger 65kDa heat-shock protein [4]. A case of TAK in association with TB has been reported from Bangladesh [5]. However, none of our patients had a history of past or present tuberculosis. Although no auto-antigen has been identified yet, the association of TAK with different human leukocyte antigen (HLA) alleles in different populations points towards a suspected aetiological association with HLA as well [6, 7]. Although other studies have reported a negative correlation between HLA alleles and Takayasu’s arteritis [8].

A few cases have been reported from Pakistan. Two case of global TAK have been reported previously, one a 55-year-old male from Rawalpindi and other was a 5-year-old girl from Skardu [9, 10]. Two cases of TAK presenting with ischemic stroke have been reported from Karachi [11].

Of the five patients we reported here, three presented in the second decade and two in the fourth decades of life. The presentation varied from cerebrovascular accident to congestive heart failure and classic symptoms of limb claudication; the most common finding among four patients was diminished or absent upper limb pulses. One patient presented with aortic dissection. Stroke is a rare presentation of TAK, as only 10–20% of patients manifest with cerebrovascular lesions. A retrospective analysis of 272 patients from South Africa, reported cerebrovascular symptoms in 20% cases of TAK [12]. The most common presentation of diminished upper extremity pulses have been reported in 88% of patients; constitutional symptoms in 66%; while cerebrovascular involvement was seen in only 18% of TAK patients [13]. Two of our patients had heart failure, although studies have reported infrequent involvement of coronary and pulmonary vasculature [14].

There is uncertainty with regards to progression of disease. There is also a poor correlation between clinical disease activity and the level of inflammatory markers in the serum [15]. Corticosteroids lead to remission in most of the patients. Many of the patients with progressive

disease show lack of response to treatment, and no convincing reports are available to reflect the long-term outcome in these patients [16]. As far as our patients are concerned, all five have so far responded well to the treatment in terms of symptomatic improvement, as well as normalization of inflammatory markers such as, ESR and CRP.

There is paucity of data from controlled, comparable trials of different treatment modalities in TAK. Different studies reported the use of different immune-suppressive drugs. No consensus has been established as to which of these drugs are to be preferred and for how long the treatment should be continued. Small open-label studies have reported the use of several immunosuppressive agents such as methotrexate, mycophenolate mofetil, and azathioprine [17–19]. Anti-TNF therapy has also been used successfully in a small number of patients [20, 21]. Our patients showed a good clinical response with steroid and azathioprine [22].

CONCLUSION

Takayasu’s arteritis (TAK) is a rare disease, with a potential for devastating clinical consequences. Clinical presentation is varied. There is a need for further studies that could establish a strategy for the use of immune-suppressive agents, monitoring disease progression and response to therapy. An immunosuppressive regimen of azathioprine and prednisolone is safe, well tolerated, and effective in ameliorating symptoms, although the appropriate duration of treatment, monitoring response and long term safety of the treatment is unclear.

Author Contributions

Tasnim Ahsan – Substantial contributions to the conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Uzma Erum – Substantial contributions to the conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Rukhshanda Jabeen – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Danish Khowaja – Acquisition of data, Analysis and the interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Urooj Lal Rehman – Substantial contributions to the conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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