ORIGINAL ARTICLE

TAKAYASU ARTERITIS: PATTERN OF CLINICAL AND RADIOLOGICAL FEATURES, EXPERIENCE FROM PAKISTAN

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Background: Takayasu arteritis (TKA) is a rare large vessel vasculitis occurring in young adults of less than 50 year of age. We analyse the clinical, radiological features, and treatment regimens in Pakistani patients presenting to a tertiary care center. **Methods:** A retrospective cross-sectional analysis of TKA patients done at the Rheumatology department of Fatima Memorial Hospital. A comprehensive evaluation of clinical, laboratory, radiographic features and treatment regimens was carried out. **Results:** A consecutive cohort of 18 patients, with 13 patients (72%) of female gender was studied. Mean age of the cohort was 35.94±2.7 years. A mean delay of 2.32±0.43 years between symptoms and final diagnosis was reported, attributed to alternate diagnosis in 57.1% and late presentation in 42.8% cases. Limb claudication (44.4%), absent pulses (38.9%), were the common initial manifestation. Hypertension (61.5%), blood pressure discrepancy between arms (88.9%) and bruit (72.2%) over major vessels were common systemic features. As per angiographic classification, Type V (44.4%), and Type I (33.3%), were most common pattern of disease in the cohort. Subclavian artery (72.2%), renal artery (33.3%), iliofemoral arteries (27.8%), and coronary artery involvement (16.7%) were the common lesions. Coronary artery lesion was higher in females (p=0.52) while renal artery lesion in males (p=0.27). There was no statistically significant difference in involvement of vessels according to gender (p >0.05). **Conclusion:** Type V and Type I are the common pattern of TKA. Limb claudication was the most common initial manifestation. Renal artery involvement was seen more commonly in males while coronary artery involvement more commonly in females.

Keywords: Takayasu arteritis; Large vessel vasculitis; Pulseless disease; Clinical and Radiological features

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INTRODUCTION

Takayasu arteritis (TKA) is a rare, granulomatous, large vessel vasculitis occurring in young adults of less than 50 year of age. The prevalence, clinical manifestation, and radiologic manifestation of TKA differ geographically and by ethnicity, with highest prevalence in Japan and other far east Asian countries.[1,2] Historically called pulseless disease due to very frequent findings of absent radial pulse, the disease clinically manifest through two phases: 1) systemic inflammatory (pre stenotic) phase with constitutional symptoms, and, 2) occlusive phase with stenosis and/or aneurysm formation and clinically manifesting with more characteristic features such as absent pulses, hypertension, kidney disease and myriad of other clinical features.[3,4] Pathologically TKA results from granulomatous inflammation of any portion of aorta, arch of aorta, its direct branches, or its bifurcation.[5] Diagnosis of TKA is made on 1990 American College of Rheumatology (ACR) criteria (Table1).
Management of Takayasu arteritis consists of Induction of remission with high doses of steroids, and immunosuppressants such as Methotrexate, and Cyclophosphamide.[6–8] Resistant or relapsed cases are treated with biologic agents like Tocilizumab.[9] Disease usually has good response to steroids and immunosuppression, morbidity occurs in form of stroke, blindness, and renal failure. There is scarcity of local data regarding presentation of this rare disease in a Pakistani Population. We present here the clinical and radiographic manifestation of this rare disease in our population to get an understanding of manifestation of this rare disease and to draw a comparison of manifestation from rest of world.

MATERIAL AND METHODS

It was a cross-sectional analysis of all TKA patients diagnosed by consultant rheumatologists in evaluated in Rheumatology department of Fatima memorial hospital (FMH) from July to December 2019. The study was approved by the institutional review board and informed consents were obtained from all patients. Demographic data including age, gender, body mass index, socioeconomic and marital status, level of education; Disease timelines such as age of

onset of illness, duration between onset of symptoms and diagnosis of TKA established, disease duration itself, initial most manifestations; Clinical features such as constitutional, systemic manifestations, and detailed vascular features were collected. In Laboratory data including CBC, renal, functions and inflammatory markers and radiographic features comprising of type of lesion, class of TKA and vessels involved (CT angiography was the radiologic investigation carried out in all cases); treatment regimens such as induction and maintenance therapy; and complications of the disease and/or treatment were recorded.

Data was analysed by SPSS using version 23.0. The categorical variables were presented in the form of frequency and percentage whereas quantitative variables were presented in the form of Mean±SD. Data was stratified according to gender and any association between gender and clinical manifestation was assessed by Chi-square or Fisher's Exact tests. *p*-value of <0.05 was considered significant.

RESULTS

Eighteen patients were included in the study during study period. Table-2 elaborates in detail the demographic and clinical features of the cohort according to gender. Sixteen (88.9%) patients were of Punjabi ethnicity. There was no association of any demographic feature with gender ($p>0.05$). Only 22% (n=4) of patients received diagnosis of TKA at their first visit. There was a mean delay of 2.32±0.43 years between onset of symptoms and final diagnosis of TKA, the delay in diagnosis was attributed to alternate diagnosis in 8 (57.1%) and to late presentation in 6 (42.8%). Interestingly, All the patients in the cohort met the ACR criteria of classification of Takayasu arteritis, with a minimum score of 4/6 (Table-1).

In descending order, the most common initial clinical manifestations or a clue to the diagnosis were; limb claudication in 8 (44.4%) patients, absent pulse in 7 (38.9%), headache and hypertension in 6 (33.3%) each, chest pain (manifested as acute coronary syndrome) and foot gangrene in 3 (16.7%) patients each, while constitutional symptoms occurred in 4 (22.2%) patients at disease onset. Both chest pain and constitutional symptoms occurred exclusively in female patients (Table-3).

Myalgias in 14 (77%) and arthralgias in 11(61%) were the most prevalent nonspecific constitutional symptoms, while fever in 3 (16.7%) and weight loss in two (11%) were present in a minority of patients. Among systemic manifestations, except for headache in 12 (61.5%) patients, and facial palsies in two (11.1%), there was no respiratory, gastrointestinal, ENT, or other neurological involvement in the cohort. Headache attribution to TKA was carried out by increased activity in other vessels and high inflammatory markers and excluding other causes such as medications, infections, and primary headache, similarly Facial palsy were localized to peripheral insult in both cases by normal brain imaging.

Cardiovascular system involvement needs elaboration. Hypertension was present in 12 (61.5%) patients. Carotidynia (pain/tenderness in neck at bifurcation of carotid artery) occurred in 3 (16.7%) patients. Blood pressure discrepancy between arms was present in 16 (88.9%) patients. Absent pulses were more prevalent in upper limbs than lower limbs (94.4% vs 22.2%). Three patients (16.7%) exclusively of female gender had coronary artery involvement. Claudication was present in 8(44.4%) patients while 3 (16.7%) patients developed extremity gangrene. Arterial Bruit were audible over following vessels in following descending order: Subclavian bruit, being most prevalent one was audible in 13(72.2%) patients, Carotid in 8(44.4%), Renal in 5 (27.8%), axillary bruit in 3 (16.7) and aortic bruit in 2 (11.1%) patients. Except for Renal bruit being more common in males and reaching a border line significance ($p=0.09$), there was no association seen in any systemic manifestation and gender.

Among Baseline laboratory features (Table-4), Females had significantly lower Hb levels as compare to males ($p=0.03$). Mean ESR was evaluated in most patients at baseline denoting increased disease activity. Although Female gender had slightly higher baseline ESR, but the difference wasn't statistically significant ($p=0.21$) (Table-4).

Analysis according to angiographic classification of vessels showed: Eight patients (44.4) had Type V TKA, 6 (33.3%) patients had type I disease, type II b and type IV was present in 2 (11.1%) each, while type IIa, and type III was not present in any patient at all (Table-5). Subclavian artery was the most commonly involved vessel in 13 (72.2%) patients followed by renal artery in 6 (33.3%), iliofemoral arteries in 5 (27.8%), abdominal aorta and axillary artery in 4 (22.2%) each, coronary artery involvement in 3 (16.7%), while thoracic aorta and celiac trunk was involved in 1 (5.6%) patient each. Except for exclusive involvement of Coronary arteries in females ($p=0.52$) and a slightly higher occurrence of renal artery involvement in males ($p=0.27$), there was no difference in involvement of these vessels according to gender. Vascular stenosis occurring in 14 (77.7%) patients was the most common type of lesion, 1 (5.5%) patient had

aneurysmal lesion while 3 (16.7%) had mix lesions (both aneurysm and stenosis).

All patients received steroids of at least 1mg/ kg/ day during active course of disease, which was gradually tapered over 3-4 months to low dose of 5mg/day. Besides, six patients (3 patients with aortic disease and 3 patients with impending gangrene) also received Pulse dose steroids of 500 mg/day for three days for high burden of disease. Methotrexate was the most common immunosuppressant agent used, in 13 (72.2%) patients, while 2 (11.1%) patients received Cyclophosphamide as induction therapy (both patients had aortic disease). Patients receiving Methotrexate experienced Gastrointestinal intolerance in 4 (31%) patients, and transient increase in liver enzymes in 3 (16.7%). No patient had to stop the drug permanently. Three (16.7%) patients in the cohort had features of iatrogenic Cushing syndrome including Diabetes development in 1 (5.6%) patient.

Two patients in CAD involvement underwent Coronary artery stenting in 1 patient underwent Coronary artery Bypass grafting for 3 vessel diseases. In addition, 1 (5.6%) patient underwent vessel clipping for axillary artery.

Table-1: 1990 American college of rheumatology criteria for classification of Takayasu Arteritis[29]

S. No.	Criteria
1.	Age of disease onset 40 years
2.	Claudication of extremities
3.	Decreased Brachial artery pulse
4.	Blood pressure difference > 1 0mm Hg
5.	Bruit over Subclavian arteries or aorta
6.	Angiographic abnormalities

A Diagnosis of Takayasu arteritis requires that at least three of the six criteria are met

Table-2: Demographic data and clinical features of Takayasu arteritis patients

Characteristics	Total n=18	Female n=13	Male n=5	*p*-value
Age	35.94±2.7	37.92±3.1	31.20±5.4	0.27
Body mass index	26.16±1.5	27.22.0	25.181.7	0.55
Smoking history	1 (6.3)	--	1 (25)	0.25
Low Socioeconomic class	10 (58.8)	6 (50)	4 (80)	0.33
Age at onset (y)	30.31±10.7	32.18±3.1	26.20±5.4	0.31
Duration of disease (y)	5.12±0.70	5.08±0.89	5.20±1.20	0.94
First Rheumatologist visit (y)	3.35±0.44	3.33±0.56	3.40±0.74	0.95
Delay in Diagnosis (Y)	2.32±0.43	2.21±0.56	2.60±0.67	0.69
Reason of delay				
Alternate Diagnosis	8 (57.1)	4 (50)	4 (50)	0.11
Late presentation	6 (42.8)	6 (100)	--	
Constitutional symptoms				
Fever	3 (16.7)	2 (15.4)	1 (20.0)	1.0
Weight loss	2 (11.1)	2 (15.4)	--	1.0
Myalgias	14 (77.7)	11 (84.6)	3 (60.0)	0.35
Arthralgia	11 (61.1)	7 (53.8)	4 (80.0)	0.59
Bruit				
Carotid	8 (44.4)	6 (46.2)	2 (40.0)	1.0
Subclavian	13 (72.2)	9 (69.2)	4 (80.0)	1.0
Axillary	3 (16.7)	1 (7.7)	2 (40.0)	0.17
Renal	5 (27.8)	2 (15.4)	3 (60.0)	0.09
Abdominal aortic bruit	2 (11.1)	1 (7.7)	1 (20.0)	0.49
Blood Pressure discrepancy	16 (88.9)	12 (92.3)	4 (80.0)	0.49
Absent pulses				
Upper limbs	17 (94.4)	13 (100)	4 (80.0)	0.27
Lower limbs	4 (22.2)	3 (23.1)	1 (20.0)	1.0
Acute coronary syndrome	3 (16.7)	3 (23.1)	--	0.52
Limb Claudication	8 (44.4)	5 (38.5)	3 (60.0)	0.60
Limb gangrene	3 (16.7)	2 (15.4)	1 (20.0)	1.0
Hypertension	12 (66.7)	8 (61.5)	4 (80.0)	0.61
Headache	12 (61.5)	8 (61.5)	4 (80.0)	0.61

Percentages given in parenthesis (). Y= years, Low socioeconomic class= Monthly income of labour class or lower in the country. Acute coronary syndrome (ACS) as clinical presentation with chest pain and ECG changes managed as per ACS protocol. Upper limb pulses include radial, ulnar, and brachial artery pulses, while lower limb pulses include dorsal pedis, posterior tibial and popliteal artery pulse. BP discrepancy= blood pressure difference of at least 20 mmHg or more of Systolic BP between two arms.

Table-3: First symptoms to present with, according to gender

Characteristics	Total	Female	Male	*p*-value
Pulselessness	7 (38.9)	6 (46.2)	1 (20.0)	0.59
Chest pain	3 (16.7)	3 (23.1)	--	--
Headache	6 (33.3)	5 (38.5)	1 (20)	0.61
Hypertension	6 (33.3)	5 (38.5)	1 (20.0)	0.61
Claudication	8 (44.4)	5 (38.5)	3 (60.0)	0.60
Gangrene	3 (16.7)	2 (15.4)	1 (20.0)	1.0
Constitutional symptoms	4 (22.2)	4 (30.8)	--	--

First symptom= clinical symptoms of presenting to physician, or a clue to diagnosis or workup, such as absent pulse or Hypertension. Pulselessness= absent pulses in either upper limbs or lower limbs. Constitutional symptoms include fever, weight loss, myalgias and arthralgias in absence of synovitis. Gangrene = gangrene of upper or lower limbs.

Table-4: Laboratory parameters at Baseline

Lab	Baseline	Female	Male	*p*-value
Haemoglobin	11.1±0.66	10.19±0.79	12.98±0.94	0.03
TLC	10.1±0.47	9.8±0.58	10.6±0.87	0.34
Platelets	290.4±27.7	293±31.0	284±61.1	0.96
ESR	53.3±5.1	58±6.2	44±8.4	0.21
ALT*	28 (24)	17.5 (23)	33 (14)	0.77
Creatinine*	0.8 (0.30)	0.8 (0.39)	1.0 (1.35)	0.78

TLC= Total leukocytes count, ESR= Erythrocyte's sedimentation rate, ALT= ALT= Alanine Transaminase, *Presented as mode (IQR)

Table-5: Angiographic classification of TKA, type of lesion and vessels involved

Characteristic	Total	Female	Male	*p*-value
Angiographic class				
Type I	6 (33.3)	5 (38.5)	1(20.0)	0.70
Type IIa	--	--	--	
Type IIb	2 (11.1)	1 (7.7)	1(20.0)	
Type III	--	--	--	
Type IV	2 (11.1)	1 (7.7)	1 (20.0)	
Type V	8 (44.4)	6 (46.2)	2 (40.0)	
Primary lesion				
Stenosis	14 (77.7)	11 (84.6)	3 (60.0)	0.32
Aneurysm	1 (5.5)	--	1 (20.0)	
Mix	3 (16.7)	1 (7.7)	2 (40.0)	
Vessels involved				
Arch of aorta	2 (11.1)	2 (15.4)	--	1.0
Thoracic aorta	1 (5.6)	1 (7.7)	--	1.0
Abdominal aorta	4 (22.2)	3 (23.1) 3 (23.1)	1 (20)	1.0
Carotid artery	3(16.7)	9 (62.2)	--	1.0
Subclavian artery	13(72.2)	3 (23.1)	4 (80.0)	1.0
coronary artery disease	3 (16.7)	2 (15.4)	--	0.52
Axillary artery	4 (22.2)	1 (7.7)	2 (40.0)	0.53
Celiac trunk	1 (5.6)	3 (23.1)	--	1.0
Renal artery	6 (33.3)	4 (30.8)	3 (60.0)	0.26
Iliofemoral artery	5 (27.8)		1 (20.0)	1.0

TKA= Takayasu Arteritis, Types of Takayasu arteritis: Type I - Branches of the aortic arch, IIa - Ascending aorta, aortic arch, and its branches, IIb -Type IIa region plus thoracic descending aorta, III-Thoracic descending aorta, abdominal aorta, renal arteries, or a combination, IV -Abdominal aorta, renal arteries, or both, Type V - Entire aorta and its branches. Mix= both stenosis and Aneurism occurring in same patient.

Table-6: Comparison of characteristics of current cohort with different global cohorts

Characteristic	Current study n=18 (Pakistan)	Goel et al n=251 (India) [18]	Comarmond et al, n=318 (French) [19]	Bicakcigil et al, n=248 (Turkey) [20]	Li J et al n=411 (China) [21]
Mean age	35.94±2.7	29.2±11.8	36*	40.1	NA
Age of onset (years)	30.31±10.7	24±11.0	NA	30.2	23*
Female: male	2.6:1	4.5:1	6:1	8.4:1	3.7:1
Angiographic type					
type I	33.3%	18%	22%	32%	22%
type IIa	--	NA	8%	6.9%	3.9%
type IIb	11.1%	NA	10%	3.2%	3.9%
type III	--	NA	5%	3.2%	2.9%
type IV	11.1%	18%	5%	3.7%	6.3%
type V	44,4%	54.2%	49%	50.8%	60.8%
Individual vessel					
Subclavian	72%		65%	76%	79.8%
Carotids	44.4%	NA	43%	52%	79.1%
Renal artery Coronaries	27.8%		23%	26%	48.9%
Aorta (abominal)	6.7%		NA	NA	3.6%
	11.1%		44%	22%	38.4%
Treatment					
Methotrexate	77.7%	8.0%	35%	63%	
Azathioprine	--	21.5%	13%	22%	NA
Cyclophosphamide	22.2%	--	3%	13%	
Mycophenolate	--	63.7%	--	4%	
Tocilizumab	--	5.6%	8.5	1.2%	

[] = Reference no in bibliography, *= Median age, NA= Data not available

DISCUSSION

The study presents an experience of TKA at a tertiary care Rheumatology center. The study has number of clinically important aspects to elaborate. To start with, this is the largest case series reporting the clinical and radiologic features of TKA in Pakistan. Despite being an Asian country, TKA literature in Pakistan is mostly confined to case reports addressing the unusual manifestations, such as stroke, association with other disease such as Tuberculosis, and Inflammatory bowel disease.[10–12]

Interestingly, the study showed a mean delay of at-least 3 years from symptoms to the diagnosis, which yields a twofold discussion. The reasons attributed to delay in diagnosis included alternate diagnoses (coronary artery disease, peripheral arterial disease, Renal artery stenosis etc to name a few) and delayed presentation. The rarity of the disease along with absence of any diagnostic antibodies, and nonspecific initial manifestations make the early diagnosis difficult. A delay of ≥1 year after onset of symptoms has been found to be resulting in severe disease burden.[13] Picking of the disease earlier in its course before any stenosis develops decrease the long-term complications including chronic kidney disease, gangrenes and other complications.[14–16] Picking up the disease (clinical features, and imaging) at this earlier, reversible and salvageable stage, provide a window of opportunity to treat earlier and hasten the total damage, as proposed by Schmidt *et al*, in their evaluation of both pre-stenotic and post-stenotic patients' evaluation.[17]

When compared to cohorts from different regions globally, our study showed characteristics concordant to overall features, but differ in certain details. Mean age, for example, was higher than Indian cohort but equal to French cohort and lower than Turkish cohort.[18–20] Female to male ratio was lowest in our cohort, followed by cohort from China, India, and highest in Turkey.[20] No of known reasons can be attributed to this variation, including genetic and geographic variations. Type V followed by Type I were the most common angiographic types in all cohorts (including current study), however, our cohort had lowest comparative percentage of type V, and highest of Type I lesion. One possible explanation of this discrepancy could be due to comparatively low female to male ratio in our study. Similarly, individual vessel involvement in the study was concordant to rest of cohorts, following the same hierarchy of subclavian vessel, followed by Carotid artery, and renal artery disease. Abdominal aortic involvement in our study was lowest among all the compared groups. In addition, coronary artery involvement per se was not reported in majority of these cohorts. Besides, treatment regime followed the same agents in all the cohorts in additive fashion from conventional to biologic agents. Methotrexate was most commonly used agent in all except Indian cohort, where Mycophenolate Mofetil (MMF) was used in vast majority. Table-6 elaborates the comparisons of the cohorts mentioned above.

The clinical features in current cohort, had a paucity of involvement other than vascular system. Except for hypertension (which is attributed to as a complication of renal artery stenosis), headache, and facial palsy, there was no other non-CVS systemic feature observed. To start with, majority of the initial most manifestations (besides constitutional symptoms) all belong to vascular insults or their sequalae. The recall bias in a retrospective analysis might be one reason of such low manifestations of non-vascular features, especially at the onset of disease. Small sample size can be considered second. The disease does manifest clinically over a wide range of symptoms, including a myriad of ischemic neurological, gastrointestinal and pulmonary manifestations.[22,23]

Interestingly, the study showed a mean delay of at-least 3 years from symptoms to the diagnosis, which yields a twofold discussion. The reasons attributed to delay in diagnosis included alternate diagnoses (coronary artery disease, peripheral arterial disease, Renal artery stenosis etc to name a few) and delayed presentation. The rarity of the disease along with absence of any diagnostic antibodies, and nonspecific initial manifestations make the early diagnosis difficult. A delay of ≥1 year after onset of symptoms has been found to be resulting in severe disease burden. (13) Picking of the disease earlier in its course before any stenosis develops decrease the long-term complications including chronic kidney disease, gangrenes and other complications.[14–16] Picking up the disease (clinical features, and imaging) at this earlier, reversible and salvageable stage, provide a window of opportunity to treat earlier and hasten the total damage, as proposed by Schmidt et al, in their evaluation of both pre-stenotic and post-stenotic patients' evaluation.[17]

Three patients had association of comorbid conditions along with TKA. One patient had Biopsy proven ulcerative colitis (UC) for 5 years, and was stable on Sulphasalazine. Association of TKA with UC has been reported in many case reports.[24,25] Terao *et al* reported at least 6.4% occurrence of UC in cases of TKA. These cases not only showed a higher expression of HLA-B52:01 gene compared to TK without UC, but also had significant earlier age of onset of TKA compared to controls.[26]

Two patients in the cohort also had history facial palsy during the disease course, with one

patient having some residual facial asymmetry. The rare, reported association of facial palsy with TKA can be attributed to both mare coexistence of two conditions at same time, and to neurologic manifestation of vasculitis itself as well.[27] The clinical response of both these conditions (Bell's palsy and vasculitis phenomenon) to steroids make the scenario even confusing.[28]

Our study has some limitations in the form of small sample size, single center study, retrospective analysis and lack of inclusion of disease activity. There is a risk of selection bias since this was not a population-based study. Despite a very small sample size, the study does give a glimpse of at least catchment area population, which is generalizable in same ethnicity.

We recommend prospective longitudinal studies with patients enrolled from multiple centers across the country and an emphasis on both clinical phenotype and genetic mapping is the need of time to provide source of more objective roadmap of this rare disorder.

In addition, to enhance the early diagnosis of TKA, we also strongly propose including a high suspicion of Takayasu arteritis in cases of unknown fever; ischemic manifestations (cardiac, peripheral vascular and cerebrovascular) with inflammatory features or absence of known risk factors; and keeping a low threshold for imaging studies (ultrasound of major neck vessels for example). This will at least decrease the delay related to alternate diagnosis. Both accurate diagnosis and early referral to specialist Rheumatologist and following a multidisciplinary approach can ensure early diagnosis with in first year of disease, well before irreversible damage and complications such as chronic kidney disease, hypertension and other adverse outcomes.

CONCLUSION

Majority of the patients in this study present late in the disease course (stenotic stage), manifesting with variable clinical manifestation. Type V and Type I are the most common angiographic types of Takayasu arteritis in our cohort. Renal artery involvement was seen more commonly in males while Coronary artery involvement more commonly in females. The results present a snapshot of this rare disease in a certain ethnic group of the country population.

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Conflict of interest: None

AUTHORS'S CONTRIBUTION

AK: Conceptualization, data collection, data analysis, manuscript writing. SA: Data collection, data analysis, manuscript writing Muhammad Haroon: Conceptualization, data analysis, manuscript writing. MZA: Data collection, data analysis, manuscript writing. RS: Data collection, data analysis, manuscript writing. ZUD: Data collection, data analysis, manuscript writing

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