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Chronic Limb Ischemia and Heart Failure in a Patient with Takayasu's Arteritis

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BACKGROUND. Takayasu's Arteritis (TAK) is a rare chronic inflammatory large vessel disease which frequently involves the aorta and/or its major branches. Progressive stenosis, occlusion and or dilatation on the vessels might result various complications such as stroke, myocardial infarction, heart failure, claudication, aortic aneurism, renal failure and pulmonary artery disease. The epidemiology of TAK is different in every country per year; USA has 2.6 cases/million, Japan 1/3000, while in Indonesia only a few were reported.[1-4]

METHODS. This observational studies in **Takayasu's** Arteritis found one case report per year in Dr. Hasan Sadikin Hospital. A 30-years old female, Indonesian nationality, Sundanese ethnic, without risk factor of peripheral artery disease. She had symptoms and signs of progressive claudication, pulseless extremity, dyspnea on effort, asymmetrical arm blood pressure, gangrene, and parese. Examination modalities were *a) MSCT angio-graphic of inferior extremity* showed right posterior tibialis artery with reconstruction in the right ankle joint, and one-third occlusion of half left posterior tibialis until left dorsalis pedia artery; *b) USG Doppler of legs* showed no flow right dorsalis pedia artery and minimal flow left dorsalis artery, and c) *Echocardiography* showed impaired systolic LV function (EF 37%) with akinetic of anteroseptal wall, hypokinetic of anterior & anterolateral walls. Based on the findings, she was diagnosed as Chronic Limb Ischemia Fontaine Stage III-IV, heart failure, sequelae of stroke infarct and hypertension. Therefore, amputation and anastomosis *bypass graft/reconstruction* of right femoralis artery to right posterior tibialis artery with saphena magna vein were done. The results of anatomic pathological femoralis artery were inflammation of tunica intima tissue followed by infiltration of fibrotic cells and calcification. The patient was treated with methotrexate, methylprednisolon, cilostazol, warfarin, bisoprolol, captopril, and amlodipine.

RESULTS. It is very difficult to diagnose TAK, currently angiography is the gold standard. Costs and facility limitations were difficulties in diagnosing TAK in this patient. Early diagnosis in this patient was based on Sharma and ACR TAK criterias. Furthermore, she had amputated and anastomosis *bypass graft/reconstruction*, and anatomic pathological results confirmed it was TAK Type 3 Nasu criteria. Although the upper extremity / coronary angiography and carotid ultrasound were not examined, but based on signs, symptoms and echocardiography might show abnormalities of the vessels such as aorta and or branches of coronary artery, carotid artery, subclavian artery, arteries and arteries brachiocephalica renalis. The complications she had were heart failure, claudication, stroke, hypertension, and asymmetrical different blood pressure. In spite, she had claudication in the lower extremities, this is a unique sign in TAK diagnosis. Chronic limb ischemia until gangrene in the lower extremities is rare. In some cases of claudication TAK more commonly occur in upper extremity than in lower extremity and rarely cause gangrene.[2-8]

CONCLUSION :TAK is a rare vasculities disease. TAK diagnosis is very difficult and needs many criterias as confirmation, one of which is through biopsy. Our case showed anatomical pathology Type 3 by Nasu TAK criteria. The unique condition in this case was chronic limb ischemia until gangrene on lower extremity, which is a rare TAK case in the world. Good management of TAK patients includes adherent treatment, prevention against progression of TAK disease, and appropriate treatment will reduce mortality, morbidity, disability, recurrence and poor complications. Comperehensive management of various multidisciplinary will result a good prognosis.[2,3,6]

Keywords : Takayasu's arteritis, Anatomic pathology, Chronic limb ischemia, Heart failure

INTRODUCTION.

This is a case report of a 30-years female who came to Hasan Sadikin Hospital with pain on the right extremities as chief complaint. Anamnesis, physical examination and imaging examinations were done such as echocardiography, MSCT of lower extremities. The results were Takayasu's arteritis with chronic limb ischemia Fontaine stage IV, heart failure and hypertension. Therefore, amputation and anastomosis bypass of the right extremity to right posterior tibialis artery with saphena magna sinistra were done. Anatomic pathology results of right posterior tialis artery and right superficial femoralis artery showed hyperplastic elastic tissue, and fibrotic cells in the middle. All the results were in accordance with Takayasu's arteritis.

About this case, we will discuss the epidemiology of Takayasu's arteritis, diagnosis, included blood vessels and further treatment of TAK.

CASE REPORT.

A 30-years old female came with pain on thr right extremity as chief complaint. The pain occurred since 3 months, especially on the right metatarsal digiti pedis III, and metotarsal IV-V grew darker (kehitaman). Since 1 year before the pain grew more after body activities such as walking that decreased after resting. She had pulseless left extremity compared with right extremity. During the last three months she stayed at home and sleep more because of fatigue that she had since 4 years before. She had weight loss and night sweating, no history of chest pain, unconscious or breathing difficulties, no history of atopy, hypertension, diabetes, smoking or high cholesterol. She never had reddish color on the cheek or skin after sun light, no hairfall, thrush, joint pain, abortion/miscarriage or contraception. She was married but without children. Amputation of right metatarsal digiti pedis I-II was done 6 years before at Advent Hospital caused by blood vessel infarction and she was given Cilotazol. Since last 2 years she had cold left arm, decreased pulse rate and asymmetric blood pressure but she could still walk.

During hospitalization in Hasan Sadikin Hospital she had pain on the right metatarsal digiti pedis III and right gangrene metatarsal digiti pedis IV-V. Pain and gangrene grew more and almost half of her right extremities grew darker. Since 2005 she was diagnosed as TAK and was treated in the outpatient department of Vascular Surgery Hasan Sadikin Hospital. She was routinely given methyl prednisolone and citostazol, but did not routinely come for control.

Physical examination. We found different blood pressure of the extremities. The right upper extremity: 140/90, left upper extremity 70/10, and no pulse rate of the lower extremities, respiration 20x/m, temperature 36.6oC, not anemic, JVP, no cardiomegaly, normal heart sound 1, heart 2 (A2P2) normal, regular, heart 3 and 4 none, no murmur, no ronchi or wheezing in both lungs, the abdomen was in normal limits.

Right arm:	Left arm:
- Pulse 80x/m, regular, equal , adequate volume - Brachial artery pulsation + - Radial artery pulsation + - Ulnaris artery pulsation + - Warm	- Blood pressure -/- - Brachial artery pulsation (+ weak) - Radial artery pulsation (-) - Ulnaris artery pulsation(-) - Cold, cyanosis

Right extremity :	Left extremity :
- Femoral artery pulsation (+ strong) - Poplitea artery pulsation (+ weak) - Posterior tibialis artery pulsation (-) - Pedis dorsalis artery pulsation (-)	- Femoral artery pulsation (+ strong) - Poplitea artery pulsation (+ weak) - Posterior tibialis artery pulsation (+) - Pedis dorsalis artery pulsation (-)

- Gangres sicca digiti III-V, dark/black, cold, cyanotic, painful (+) III-V
- Fore foot post amputation digiti I-II
-

Neurologic examination. SO, round pupil isocor, diameter ODS 3 mm, RC +/+; face (slight left central paresis NVII), tongue paresis left central), motoric (right 4/sdn, left 4/4), decreased left sensoris.

Laboratory examination. Hemoglobin 10.6 gr%, Leucocyte 10.600/mm3, Hematocrit 34%, Thrombocyte 602,000/mm3, Ureum 10 mg/dl, Kreatinine 0.46 mg/dl, Natrium 130 mEq/dl, Kalium 3.8 mEq/dl, GDS 130, LED 110/136, CRP 93.3, ANA non reactive, SGOT 13, SGPT 10, INR 2.52.

Electrocardiography. Sinus rhythm, normal**.**

Thorax photo. Cardomegaly, no lung TB.

Figure 1. Thorax photo.

Figure 2. Echocardiography.

MSCT Inferior extremity angiography using 3D on May 26, 2011, showed normal artery iliaca, femoralis and bilateral poplitea; stenosis on the right posterior tibialis artery with reconstruction on the right ankle joint and occlusion on the left middle 1/3 posterior tibialis artery up to left pedis dorsalis artery. Reluts: peripheral artery disease.

Doppler USG of extremity. No flow on the right pedia dorsalis artery and there is still minimal flow on the left pedis dorsalis artery.

Figure 3. MSCT Angiography of inferior extremity.

The result of **echocardiography** on June 7, 2011, showed impaired systolic LV function EF 38.7%; diastolic dysfunction grade III, akinetic anteroseptal, anterior and anterolateral hypokinetic, SEC on the LV (+) and MR mild and AR mild.

The patient was diagnosed as Takayasu's arteritis, occlusion of right arteries. Poplitea + gangren metatarsal III-V pedia dextra (Chronic limb ischemia fontaine grade III-IV), heart failure, hypertension and stroke sequellae.

Then amputation and anastomosis bypass reconstruction of right femoralis artery to right posterior tibialis artery with saphena magna vein was done. The result of anatomic pathological of the right superficial femoralis showed hyperplastic tissues followed by fibrotic cells and calcification that were in accordance with (that indicated) Takayasu 's arteritis.

Figure 4. The anatomic pathological result of right femoralis artery showing fibrosis on the intima tunica

During hospitalization the patient was given immunosupressive therapy with 25 mg methotrexate weekly, then decreased to 2.5 mg weekly for 3 months, corticosteroid methyl prednisolone (0.8 mg/KgBW/24 hrs), 32 mg for 3 months, cilostazol 2x100 mg, aspirin 1x81 mg po, warfarin 4 mg po, bisoprolol 1x5 mg po, captopril 3x25 mg po, amlodipin 1x10 mg po, folic acid 1x5 mg po, calos 3x1. The patient was suggested to do MSCT angiography on the upper extremity, heart and the branches such as coronary artery, carotid artery, subclavia, brachiocephalia and renalis, but none of the examinations was done because of cost and facility limitation.

DISCUSSION.

The patient was a young female aged 30 years, Indonesian nationality, Sundanese ethnic, without risk factor of vasculitis or peripheral artery disease. Her characteristics were in accordance with TAK prevalence mostly found in Japan, India, Southeast Asia. Females are 10 times more than males in the third decade. TAK is a rare chronic inflammatory of large vessel disease. The epidemiology is different in each country per year; America 2.6 per million, Japan 1 per 3000, while in Indonesia only several cases were reported. The etiology in this patient were still unknown, while several studies of TAK in Asian race (Japan, Southeast Asia, India) and South America showed HLA characteristics: B52, B39, DRB, DQB, and DPB. Up to now we have no data about the kind of HLA of TAK patients in Indonesia because of cost limitation.

In this patient we found the criteria of vasculitis based on the literature on ACR and Vascular Companion Braunwald:

1. Female, age 30 years, Southeast Asian ethnic.
2. Complaint (pain on extremity for months, cold left arm and leg, weak left pulse rate, constitutional symptoms (decrease of appetite), weight loss, night sweating, no risk factor of blood vessel disease.
3. The sign (asymmetric difference of blood pressure on right and left arms, no pulsation, gangren, paresis).
4. Laboratory examinations: (anemia, increased CRP and LED, negative ANA test).
5. Additional examinations: MSCT, echocardiography, and Doppler ultrasonography (anomalies that include nearly all systemic body organs).

Based on the anamnesis, physical and additional examinations, we were suspicious about vasculitis anomalies of the great vessels, i.e. Takayasu 's arteritis. The next table shows the type of vasculitis based on the blood vessel diameter.

Table 1. Grouping of vasculitis based on the size of blood vessel.

There are several developments in diagnosing TAK. The first classification of TAK was made by Ishikawa in 1978, American College of Rheumatology (ACR) in 1990, Sharma in 1995 based on angiographic criteria. The diagnosis in this patient was based on Sharma and ACR 1990 (Table 2 and 3). Data of this patient were based on Sharma criteria, were:

a. One (1) major criteria (symptoms of intermitent claudication of lower extremity).
b. Three (3) minor criterias (hypertension, high ESR, echocardiography with probability of coronary artery anomalies).

Table 2. Diagnosis of Takayasu 's arteritis based on Sharma criteria.

Besides the Sharma criteria, we found in this patient 4 out of 6 criterias of TAK according to the American College of Rheumatology, i.e.

a. Age below 40 years with progressive symptoms related to TAK .
b. Complaints of progressive claudication.
c. Decreased brachial arterial pressure of more than 10 mmHg and the difference of more than 10 mmHg with the other arm.
d. Worsening of pulsation on the brachial artery area.

There were two uncovered criterias : a) auscultation to find out whether there was bruit on the subclavical artery or abdominal aorta; b) arteriography or angiography of the aorta and the main branches of the upper extremity.

Table 3. Classicication of Takayasu 's arteritis based on the American College Rheumatology.

According to Nasu criteria and based on anatomic histology there are 3 types of Takayasu 's arteritis, and our patient was in Type 3. Anatomic pathology result in this patient showed inflammation of the intima tunica tissues followed by infiltration of fibrosis and at last calcification.

The diagnosis of TAK in this patient was not completely set up because we did not do the needed additional examinations such as MSCT cardiac angiography, aorta (thorax, abdomen and upper extremity branches), caroti ultrasonography, head CT scan as well as opthalmologic consultation.

From the anamnesis, physical and echocardiographic examinations we found out symptoms (hypertension, asymmetric different blood pressure, decreased and asymmetric pulsation of right and left veins, and stroke sequellae); complaints (**anesthesia** or cool left arm, and fatigue), echocardiography (akinetic anteroseptal, anterior and anterolateral hypokinetic). Those data indicated the possibility of anomalies of the veins and its branches such as coronary artery, karotid artery, subclavian artery, brachiocephalica and renalis arteries. Other examination we did not performed were bruit, karotid USG and consultation to opthalmologist.

We found in this patient chronic limb ischemia fontaine grade III-IV on the inferior extremity. In Takayasu 's arteritis, we seldom find anomalies of the vein vessel of inferior extremity compared to superior extremity, aortic branches or renal artery. A study on TAK in Italy found out claudication of the upper extremity 62% and 32% of the lower extremity accompanied by pulsus deficit of upper extremity 53% and lower extremity 15%. A study in Brazil by Panico on 36 TAK patients showed claudicaton of upper extremity 69.5% and 30.5% of lower extremity. This study (by Panico) stated that the related blood vessels were karotid artery 47.2%, aorta 19.4%, subclavicula artery 13.8% and renal artery 8.3%. Rosli in his study on 65 TA patients in Institut Jantung Negara Malaysia found out anomaly on the coronary artery 3, mesenteric artery 5, celiac artery 2, renal artery 16, iliac aorta 11, subclavian artery 2, and axillaris artery 4. TAK patients in Japan had more related blood vessels with pulseless radial artery and ischemia of cervical artery, while in China Korea and India, TA patients had related more on abdominal aorta including renal artery.In Indonesia we had no data on the related blood vessels of TAK patients. While in this patient the anomaly was related to almost all of aortic branches according to anamnesis, physical examination and additional examinations as we discussed before.

The aim of therapy of Takayasu 's Arteritis is to make a pressure on the inflammation and prevent irreversibel damage of blood vessels. The therapy could be medical, and surgery or non surgery intervention.

Table 4. Distribution of blood vessel lesions in TAK population in India and Japan.

In our study the patient had repeated active onset. The criteria that show the repeated onset of active TAK were:

a. Repeated claudication on the legs, asymmetric blood pressure of the arm, pulseless left arm and carotodynia.
b. Increased ESR.
c. MSCT angiography of inferior extremity showed occlusion.
d. Related systemic complaints (fever, weight loss) that were unexplainable for other diseases.

Medical therapy is different in patient with first onset **or repeated onset of active Takayasu 's arteritis**. Our patient was diagnosed as TAK since 2005. On admission to Hasan Sadikin Hospital she had recurrent active onset. Therefore, the immunosupressant she got was different with that in the first active onset of TAK. Immunosuppressant given for recurrent TAK is methotrexate. Methotrexate is used to increase the

healing (perbaikan) of the blood vessels, stabilize refractory or relapse of repeated onset of TAK, drug of choice for large inflammation of blood vessel, and less side effect compared to cyclophosphamide. Our patient was also given corticosteroid of methyl prednisolon group to stabilize the inflammation and longer effect of the onset (24 hours). Other medical therapy were for chronic limb ischemia, heart failure and hypertension were cilostazol, warfarm, captopril, bisoprolol and amlodipin.

Intervention therapy for TAK consists of surgery and nonsurgery based on the grade of occlusion, stenosis, aneurism of the blood vessels.Our patient had chronic limb ischemia grade III-V, therefore we performed surgery intervention as indicated by peripheral limb ischemia (gangren) on metatarsal III-V. Afterwards we did amputation on regio dorsalis pedis metatarsal digiti III-V dextra and anastomosis bypass of right femoral artery to posterior tibial artery by vena saphena magna sinistra. Bypass/ reconstruction procedure in TAK is only performed when percutaneous transluminal angiography (PTCA) is difficult to perform. A study on 50 patients performed the bypass; 24% of the patients had restenosis and 4% had thrombosis caused by bypass graft. But the disadvantage of bypass procedure is often related to the high morbidity, high body disability, restenosis, thrombosis and recurrence relaps after medical therapy.

The aim of non surgery intervention in TAK is to prevent severe complication. The study by Sharma et al, found 82% TAK patients grew better after Percutaneous Transluminal Angioplasty (PCTA). Tyagi er al, performed successfully PCTA on 89% patients; 79% of which were followed up for 43 months without any complications. The results of study by Tyagi and Sharma showed that PTCA indicated successful management of stenosis on TAK patients. In our patient we did not do screening on anomalies of upper branches of blood vessels such as coronary artery, carotid artery, subclavicule artery, brachiocephalia and renal artery, so we could not perform PTCA. More over we had no data about non surgery intervention on previous TAK patients in Hasan Sadikin Hospital.

Hypertension is a rare complication in TAK patients. We had to make consideration about renal artery stenosis in our patient, but screening MSCT on renal blood vessels was not performed in our patient. Complication that might cause mortality is heart failure, miocardiac infarct, aortic aneurism rupture and renal failure. According to a report by Lupi-Herrera et al, 15% mortality of TAK were caused by heart failure. A cohort study in India on 88 TAK patients with heart failure showed survival rate of 5 years (91%) and 10 years (84%). One of the mortality causes was found in our patient, i.e. heart failure, therefore, we need a right/proper management to minimize the risk of mortality in her.

A good management in our patient must include discipline/obedience in therapy, prevent the progressivity of the disease and the right/proper therapy to minimize mortality, disability, and recurrence.

CONCLUSION.

Takayasu's Arteritis is a rare vascular disease. The diagnosis might be made based on several kinds of criteria. Complete additional examinations need to be performed to make the right diagnosis and adequate therapy, even with only minimal additional examination. Our patient had repeated active onset of Takayasu 's Arteritis. A good management in our patient must include discipline/obediance in therapy, prevent the progressivity of the disease and the right/proper therapy to minimize mortality, disability, and recurrence. Our patient needs a comprehensive multidisciplinary management, i.e. rheumatologist, vascular, cardiologist, opthalmologist, neurologist, and vascular surgery.

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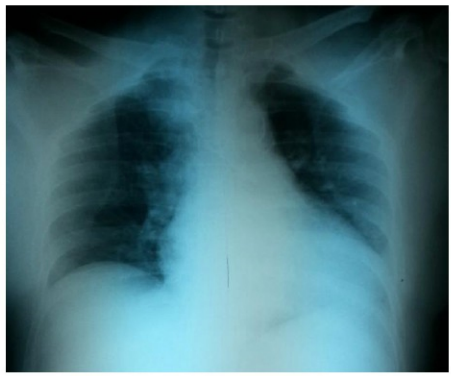
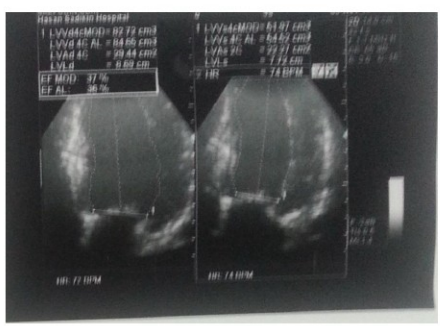


Figure 1. Thorax photo.



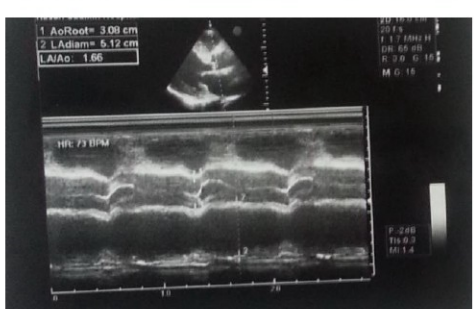


Figure 2. Echocardiography.

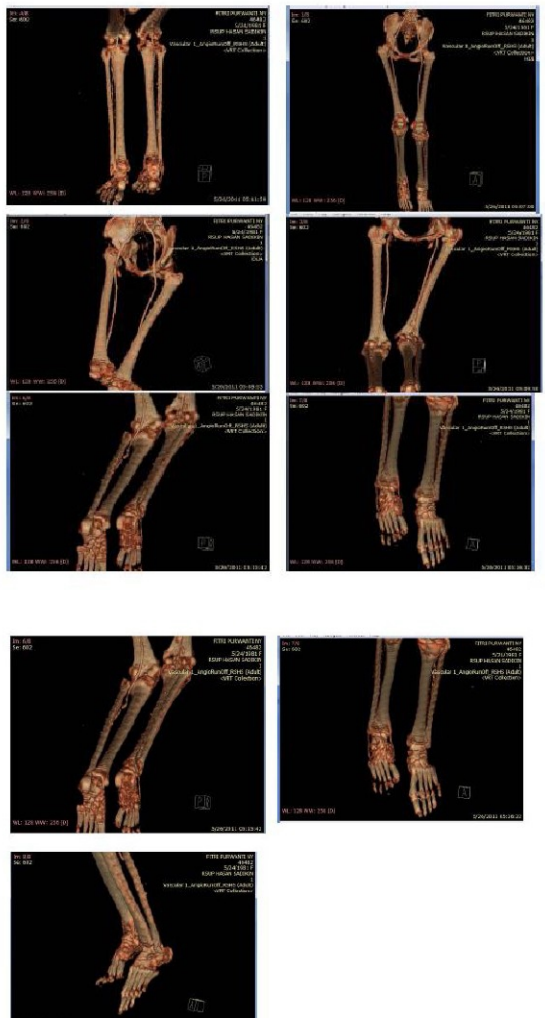


Figure 3. MSCT Angiography of inferior extremity.

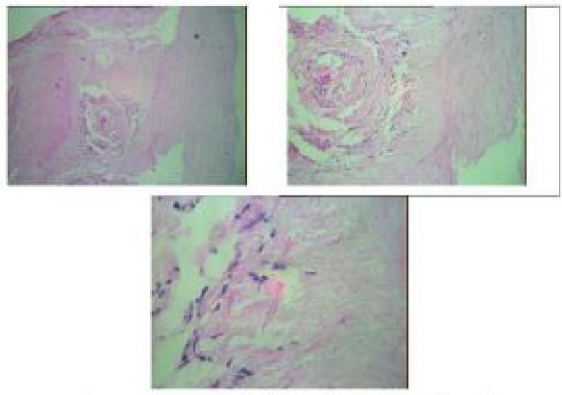


Figure 4. The anatomic pathological result of right femoralis artery showing fibrosis on the intima tunica

Pembuluh Darah Besar	Pembuluh Darah Sedang	Pembuluh Darah kecil
- Giant cell arteritis	- Polyarteritis nodosa	- Henoch Schonlein purpura
- Takayasu's arteritis	- Wegener's granulomatosis	- Cryoglobulinemic vasculitis
- Behcet's disease	- Microscopic polyangitis	- Primary angiitis of the CNS
- Relapsing polychondritis	- Churg Strauss syndrome	- Goodpasture's syndrome
- Cogan's syndrome	- Kawasaki disease	- Rheumatoid arthritis
- Aortitis associated with spondyloarthropaties		- Systemic Lupus
- Retroperitoneal fibrosis		
- Idiopathic aortitis		

Table 1. Grouping of vasculitis based on the size of blood vessel.

Modified Diagnostic Criteria for Takayasu's Arteritis*

Three major criteria:	
1. Left mid subclavian artery lesion	The most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography
2. Right mid subclavian artery lesion	The most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice to the point 3 cm distal to orifice determined by angiography
3. Characteristic signs and symptoms of at least one month duration	These include limb claudication, pulselessness or pulse differences in limbs, an unobtainable or significant blood pressure difference (>10 mm Hg systolic blood pressure difference in limb), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnoea or palpitations.
Ten minor criteria	
1. High ESR	Unexplained persistent high ESR. > 20 mm/h (Westergren) at diagnosis or presence of the evidence in patients history
2. Carotid artery tenderness	Unilateral or bilateral tenderness of common arteries on palpation. Neck muscle tenderness is unacceptable.
3. Hypertension	Persistent blood pressure > 140/90 mmHg brachial or > 160/90 mmHg popliteal
4. Aortic regurgitation or Annuloaortic ectasia	By auscultation or doppler echocardiology or angiography. By angiography or two-dimension echocardiography.
5. Pulmonary artery lesion	Lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy, or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or in unilateral or bilateral pulmonary arteries determined by angiography.
6. Left mid common carotid lesion	Presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography.
7. Distal brachiocephalic trunk lesion	Presence of the most severe stenosis or occlusion in the distal third determined by angiography
8. Descending thoracic aorta lesion	Narrowing, dilation or aneurysm, luminal irregularity or any combination determined by angiography; tortuosity alone is unacceptable.
9. Abdominal aorta lesion	Narrowing, dilation or aneurysm, luminal irregularity or aneurysm combination.
10. Coronary artery lesion	Documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus

Note: The presence of two major or one major and two minor criteria or four minor criteria suggests a high probability of Takayasu's arteritis.

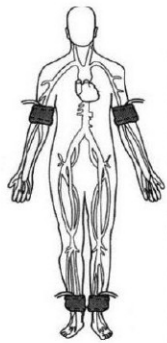
* Sharma et al., 1995.

Table 2. Diagnosis of Takayasu 's arteritis based on Sharma criteria.

(i) Age <40 years old: development of symptoms or signs related to TAK at age <40 years.
(ii) Claudication of extremities: development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities.
(iii) Decreased brachial arterial pulse: decreased pulsation of one or both brachial arteries.
(iv) Blood pressure difference >10 mmHg: difference of >10 mmHG in systolic blood pressure between arms.
(v) Bruit over subclavian: bruit audible on auscultation over one or both arteries or aorta subclavian arteries or abdominal aorta.
(vi) Arteriogram abnormality: arteriographic narrowing or occlusion of the entire aorta, its proximal branches or large arteries in the proximal upper or lower extremities, not due to atherosclerosis, fibromuscular dysplasia or similar causes; changes usually focal or segmental.

Note that for the purposes of classification a patient shall be said to have TAK if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and specificity of 97.8%. Reproduced from[11].

Table 3. Classicication of **Takayasu 's arteritis based on the American College Rheumatology.**



	Japan	India	P Value
Ascending aorta	34	9	P < 0.01
Aortic arch	14	19	NS
Descending thoracic aorta	36	29	P < 0.05
Brachiocephalic artery	22	15	P < 0.05
Vertebral artery (right/left)	26 (16/10)	10 (3/7)	P < 0.01
Subclavian artery (right/left)	67 (25/42)	86 (26/60)	NS
Common carotid artery (right/left)	68 (29/39)	30 (11/19)	P < 0.01
Abdominal aorta	38	75	P < 0.05
Renal artery (right/left)	27 (13/14)	122 (59/63)	P < 0.01
Celiac artery	1	7	NS
Superior mesenteric artery	5	15	NS
Inferior mesenteric artery	2	3	NS
Iliac artery (right/left)	0	28 (16/12)	P < 0.01
Total	340	448	

Table 4. Distribution of blood vessel lesions in TAK population in India and Japan.