

Takayasu's arteritis: A case report and a brief review of the literature

OLIVIA MANFRINI, RAFFAELE BUGIARDINI

Department of Internal Medicine, Cardioangiology, Hepatology, Alma Mater Studiorum University of Bologna - Italy

ABSTRACT: *Takayasu's arteritis primarily affects young women. The current case report focuses on a Caucasian middle-aged woman who complained of weakness, malaise, and fatigue for as many as 19 years. Delayed diagnosis and lack of specific treatment could explain the extent and the clinical severity of the disease at time of hospital admission. Angiography showed focal narrowings of the abdominal and thoracic aorta and occlusion of both the subclavian arteries, of the right coronary artery and severe stenosis of the first marginal obtuse. Takayasu's arteritis is not limited to women of Japanese origin but is present worldwide. Early diagnosis and treatment is warranted. Outcome appears to be favorable when the disease is quiescent. (Heart International 2006; 2: 66-71)*

KEY WORDS: *Takayasu's arteritis, Inflammatory arteritis, Subclavian artery, Coronary artery*

CASE REPORT

A 54-year old Caucasian woman was admitted to hospital because of severe acute pulmonary edema. She had a 20-year history of hypertension, but recently all medications were discontinued because of an episode of syncope and a finding of very low arterial pressure (95/60 mmHg in the right arm). She complained of previously formless symptoms, such as malaise, weakness, fatigue and fever. Symptoms had presented occasionally since she was 35-years old. A relapse of these symptoms occurred 2 weeks before admission.

At physical examination there was a remarkable blood pressure discrepancy between the right and left arms. Blood pressure was undetectable in the left arm, but was 95/60 mm Hg supine in the right arm. Both the left radial and left brachial pulses were impalpable. Other significant findings include the following. She had a heart rate of 100 beats per minute, and a body temperature of 37.9°C. There was an III/IV systolic murmur along the right sternal border and a diastolic blowing murmur over the left. Chest auscultation revealed rales

and rhonchi, bilaterally. Subsequent chest radiography demonstrated bilateral infiltrates and a modest bulge on the third arch of the left heart border. T wave inversions from V2 to V6 were seen at ECG. Trans-thoracic echocardiography was, therefore, performed and documented a mild aortic regurgitation, and inferior and lateral wall motion abnormality. The moderately low ejection fraction (50%) could not explain the severe clinical picture. Positive laboratory findings included elevated erythrocyte sedimentation rate (45 mm/1st h) and C-reactive protein levels (5.3 mg/dL). Blood cultures, venereal disease research laboratory test, and autoimmune serological findings were negative. Left and right heart catheterizations were performed through the right femoral approach. Recording of systolic aortic pressure showed values up to 250 mmHg. The left and right subclavian arteries were occluded and there was moderate pulmonary hypertension (pressure 66 mmHg systolic). The other angiographic findings were as follows: focal narrowings of the abdominal and thoracic aorta as well as severe calcification in the whole aorta; ostial occlusion of the right coronary artery and severe stenosis of

the first (90% stenosis) marginal obtuse. Two stents in the marginal obtuse were successfully placed (residual stenosis <20%). She was treated with oral methylprednisone (40 mg/day), clopidogrel, and diuretics (furosemide 25 mg/day). Inflammatory parameters normalized within 3-weeks. She was discharged from hospital. Methylprednisone was gradually reduced at a maintenance dosage of 12 mg/day. She remained free of symptoms. At 6 month follow-up the patient was still asymptomatic.

DISCUSSION

Takayasu's disease is a chronic inflammatory disease of large- and medium-sized arteries, involving the aorta and its main branches, the pulmonary arteries, and the coronary tree. Since the original report of Takayasu's disease in 1908 (1), the estimated worldwide incidence is 2.6 cases per million per year, with women more commonly affected than men. Peak onset is in individuals in their 30s. The disease has been mainly studied in Japan but Western studies have also been published (2-8). Cardiac features are present in up to 40% of cases. Patients usually have no risk factors for atherosclerosis and yet have atheromatous aorta, suggesting the importance of inflammation in atherosclerosis (9).

Vascular changes lead to main complications, including hypertension, most often due to renal artery stenosis or, more rarely, stenosis of the suprarenal aorta; aortic insufficiency due to aortic valve involvement; pulmonary hypertension, and aortic or arterial aneurysm (10, 11). Cardiomyopathy, myocarditis, and pericarditis have been also reported (10). Patients with pulmonary arteritis may develop pneumonia, interstitial pulmonary fibrosis, and alveolar damage (12). Other clinical manifestations include vertebrobasilar ischemia, carotid stenosis, and hypertensive encephalopathy (13). Takayasu's disease has also been associated with inflammatory bowel disease, glomerulonephritis, systemic lupus, rheumatoid arthritis, and ankylosing spondylitis (14, 15). Less common associations have been seen with sensorineural hearing loss (16). The retinopathy originally described by Takayasu's is seen in only about one-quarter of patients and is usually associated with carotid artery involvement (17).

Causes and pathophysiology

The etiology of the disease remains unknown. Tuberculosis was proposed as a predisposing factor (11, 18, 19). Patients with Takayasu's arteritis were found to have higher immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) titers against the *M tuberculosis* extract than control patients (20). Accordingly, recent work reported the presence of CD3⁺ T cells and IgG antibodies reactive to circulating antimycobacterial heat shock protein 65 (mHSP65) antibodies and to its human homologue, hHSP60 (21). However, these data appear to be in contradiction with other observations. In a series of 17 children, none had active tubercular lesions (22). Cutaneous hypersensitivity to tubercular protein was seen in only 35.2% of cases (22). Various other mechanisms such as autoimmunity and genetic predisposition have been proposed (23). Both cellular and humoral factors are probably involved. Autoimmunity appears to be the most plausible mechanism. Defective T lymphocyte regulation and anti-endothelial, anticardiolipin, and antiaorta antibodies have been suggested to play a role in the etiology of the disease (24-26). The precise nature of the antigens needs to be identified.

Patient history and physical examination

Takayasu's arteritis usually progresses through stages. The first stage is an early systemic stage during which the patient may complain of formless symptoms. Fatigue, malaise, and fever are the most frequently encountered early symptoms. This stage is considered to be prevasculitic. The second stage is concurrent with the vascular inflammation. Symptoms characterizing this stage include pain in extremities, dyspnea, palpitations, headaches, rash (more often erythema nodosum), hemoptysis, ulceration, and weight loss. Other symptoms may include arm numbness, claudication in the legs, double vision, amaurosis fugax, stroke, transient ischemic attacks, hemiplegia, and paraplegia. The third step is the burned-out stage, when fibrosis sets in, and is generally associated with remission of symptoms. The formless systemic symptoms and vascular symptoms may occur at the same time.

A detailed careful physical examination, and appro-

ropriate laboratory tests are needed in all cases to determine the type of onset, course of illness, organ systems affected, and extent of involvement. The main finding is absent pulse(s) or a pulse discrepancy of greater than 10 mm Hg between the right and left arms. Other significant signs include vascular bruits, focal neurologic deficits, hypertension, retinal ischemia and microaneurysms, eclampsia, subarachnoid hemorrhage leg edema, heart failure, and rarely, anginal symptoms.

Laboratory tests

Laboratory tests tend to be nonspecific. The erythrocyte sedimentation rate may be high, generally greater than 50 mm/h, in early disease but it is often paradoxically normal later. Leukocyte count may be normal or slightly elevated. A moderate, normochromic anemia may be present in patients with advanced disease. Autoantibodies observed in other connective tissue diseases, including antinuclear antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibodies are as common as in the general population. Hypoalbuminemia and increased levels of fibrinogen, C reactive protein, and gamma globulin are frequent findings. HLA typing has not confirmed any definite association.

Imaging

Angiography is the criterion standard (11, 27, 28). Angiographic criteria must show narrowing of the aorta, its primary branches, or large arteries in the proximal upper or lower extremities. Changes are usually focal or segmental. Angiographic classification allows a comparison of patient characteristics according to the vessels involved and is helpful in planning surgery, but they offer little by way of prognosis (28). Computed tomography (CT) scanning or ultrasound may be used to assess the thickness of the aorta (29). Magnetic resonance (MR) can be used to noninvasively assess the vasculature, but it is less accurate (30). Ultrasonography, and gallium as well as whole-body positron emission tomography (PET) scanning may provide useful information to assess the degree of inflammatory involvement of the vessels (31-33). The additional value of these new techniques in the diagnosis and follow-up of patients with Takayasu's arteritis needs further validation.

Diagnosis

Diagnosis of Takayasu's arteritis is often delayed or even missed because this disease has a non-specific clinical presentation. Ishikawa's criteria (2) (Tab. I) and those of the American College of Rheumatology (27) are both reliable clinical tools (Tab. II). Given the heterogeneity of the disease depending upon geographic location, it is not surprising that none of the criteria have universal applicability. Hence, Sharma et al (34) have proposed modifications as follows: (a) removal of age less than 40 years; (b) inclusion of signs and symptoms as a major criteria; (c) removal of age in the definition of hypertension; (d) deletion of the absence of aorto-iliac lesion in defining abdominal aortic lesion and (e) in addition, inclusion of coronary artery lesion in absence of risk factors.

Treatment

Medical management depends on the disease activity and the complications that are present. Some patients have only mild forms of Takayasu's arteritis; others deteriorate considerably. The two most important goals of treatment are controlling the inflammatory process and controlling the hypertension. Corticosteroids are the most important therapeutic agents and are necessary in active disease. Therapy is continued until patients achieve remission. For patients who do not achieve remission on corticosteroids, cytotoxic agents such as methotrexate or cyclophosphamide may prove effective; azathioprine is another possible option. For relapses, combinations of the above can be used.

Hypertension is treated with antihypertensive agents, and aggressive therapy is necessary to prevent complications. Antiplatelet agents and heparin may prove useful in preventing stroke.

Few procedures are necessary. Grafts have been used to bypass regions of severe stenosis or occlusion (23). Usually, the graft is a saphenous vein graft. Extraintracranial bypass operations generally are executed for stenosis of the internal carotid or middle cerebral arteries. Percutaneous transluminal coronary angioplasty has been performed in a few cases (32, 35). Information about outcome is, therefore, limited.

TABLE I - ISHIKAWA'S CRITERIA FOR THE DIAGNOSIS OF TAKAYASU'S ARTERITIS (Ref. 2)

Criteria	Definition
Obligation criterion	
Age < 40 year	Age < 40 year at diagnosis or onset of characteristic signs and symptoms of 1 month duration in patient history
Two major criteria	
1) Left mid subclavian artery	The most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the left vertebral artery orifice 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 that 3 cm distal to the orifice determined by angiography.
Nine minor criteria	
1) High ESR	Unexplained persistent high ESR >20 mm/h (Westergreen) at diagnosis or presence of evidence in patient history.
2) Carotid artery tenderness	Unilateral or bilateral tenderness of common carotid arteries by physician palpation; neck muscle tenderness is unacceptable.
3) Hypertension	Persistent blood pressure > 140/90 mmHg brachial or >160/90 mmHg popliteal at age < 40 year. Or presence of history at age < 40 year.
4) Aortic regurgitation or annuloaortic ectasia	By auscultation or Doppler echocardiography or angiography.
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 most severe stenosis or occlusion in the mid portion of 5 cm in the length from the point 2 cm distal to its orifice determined by angiography.
7) Distal brachiocephalic trunk lesion	Presence of most severe stenosis or occlusion in the distal third lesion determined by angiography
8) Descending thoracic aorta lesion	Narrowing, dilatation or aneurysm, luminal irregularity or any lesion combination determined by angiography; tortuosity alone is unacceptable.
9) Abdominal aorta lesion	Narrowing, dilatation or aneurysm, luminal irregularity or any combination and absence of lesion in aorto-iliac region consisting of 2 cm of terminal aorta and bilateral common iliac arteries determined by angiography; tortuosity alone is unacceptable.

The proposed criteria consist of one obligatory criterion, two major criteria, and nine minor criteria. In addition to the obligatory criterion, the presence of major criteria, or of one major and two or more minor criteria or of four more minor criteria suggests a high probability of the presence of Takayasu's disease

TABLE II - CRITERIA OF AMERICAN COLLEGE OF RHEUMATOLOGY FOR THE CLASSIFICATION OF TAKAYASU'S ARTERITIS (Ref. 27)

Criteria	Definition
Age at disease onset in year	Development of symptoms or findings related to Takayasu's arteritis at age <40 years.
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities.
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries.
Blood pressure difference >10 mmHg	Difference of >10 mmHg in systolic blood pressure between arms.
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta.
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibro-muscular dysplasia, or similar causes: changes usually focal or segmental.

For purposes of classification, a patient shall be said to have Takayasu's arteritis 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 a specificity of 97.8%

Focus on coronary arteries

The incidence of coronary artery involvement has been reported to be 9% to 10% (36). It is recognized mainly at autopsy because angina pectoris is rarely a presenting feature. It has been reported only in 6-16% of cases (17, 37). Pathology often documents intimal fibrous thickening and typical atheromatous lesions. Advanced lesions demonstrate a panarteritis with intimal proliferation. In these cases, prominent features are medial smooth muscle and elastic lamina destruction, with medial and adventitial cell infiltration and fibrosis (9). Lesions produced by the inflammatory process can be stenotic, occlusive, or aneurismal. Stenotic or occlusive lesions are often located at the coronary ostia or at the proximal segments of the arteries. Narrowing of the coronary arteries is mainly due to the extension of the inflammatory processes from the ascending aorta. Aneurysmal lesions may have areas of arterial narrowing. Most of the coronary artery lesions in Takayasu's arteritis are stenotic or occlusive. Coronary aneurysms

seem to be very rare in Takayasu's disease. Inflammation may diffusely involve the entire epicardial arterial tree. Distinction of coronary narrowing due to atherosclerosis by narrowing due to focal coronary arteritis is often difficult. Treatment of the coronary disease is still problematic. Because Takayasu's arteritis is rare, data on mortality and morbidity are limited.

CONCLUSION

Takayasu's arteritis should be considered in women with a history of weakness, malaise, and fatigue. This case illustrates the consequences of a delayed diagnosis.

Address for correspondence:

Olivia Manfrini, MD
Dipartimento di Medicina Interna, Cardioangiologia, Epatologia
Alma Mater Studiorum University of Bologna
Via Massarenti, 9 (Padiglione 11)
40139 Bologna - Italy
olivia.manfrini@unibo.it

REFERENCES

1. Ohta K. Ein seltener, Fall von beiderseitigem. Carotis-subclavia verschluss: ein beitrag zur pathologie der anastomosis peripapillaris des auges mit fehlendem. *Trans Soc Pathol Jpn* 1940; 30: 680-90.
2. Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's's arteriopathy. *J Am Coll Cardiol* 1988; 12: 964-72.
3. Koide K. Takayasu's arteritis in Japan. *Heart Vessels Suppl* 1992; 7: 48-54.
4. Nakao K, Ikeda M, Kimata S, Niitani H, Niyahara M. Takayasu's's arteritis: Clinical report of eighty-four cases and immunological studies of seven cases. *Circulation* 1967; 35: 1141-55.
5. Zheng D, Fan D, Liu L. Takayasu's arteritis in China: A report of 530 cases. *Heart Vessels Suppl* 1992; 7: 32-6.
6. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. *Ann Intern Med* 1994; 120: 919-29.
7. Lande A, Bard R, Rossi P, Castrucci A. Takayasu's arteritis: A worldwide entity. *NY State J Med* 1976; 76: 1477-82.
8. Numano F. Differences in clinical presentation and outcome in different countries for Takayasu's arteritis. *Curr Opin Rheumatol* 1997; 9: 12-5.
9. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. *J Clin Pathol* 2002; 55: 481-6.
10. Sharma BK, Jain S, Sagar S. Systemic manifestations of Takayasu arteritis: The expanding spectrum. *Int J Cardiol* 1996; 54 (suppl): S149-54.
11. Lupi-Herrera E, Sanchez-Torres G, Marcusshamer J, Mispireta J, Horwitz S, Vela JE. Takayasu's arteritis. Clinical study of 107 cases. *Am Heart J* 1977; 93: 94-103.
12. Kreidstein SH, Lytwyn A, Keystone EC. Takayasu arteritis with acute interstitial pneumonia and coronary vasculitis: Expanding the spectrum. Report of a case. *Arthritis Rheum* 1993; 36: 1175-8.
13. Rath PC, Lakshmi G, Henry M. Percutaneous transluminal angioplasty using a cutting balloon for stenosis of the arch vessels in aortoarteritis. *Indian Heart J* 2004; 56: 54-7.
14. Masuda H, Ishii U, Aoki N, et al. Ulcerative colitis associated with Takayasu's disease in two patients who received proctocolectomy. *J Gastroenterol* 2002; 37: 297-302.

15. Kubasiewicz E, Rydlewska-Sadowska W, Plachecka-Gutowska M. Takayasu syndrome with symptoms of systemic lupus erythematosus and rheumatoid arthritis. *Reumatologia* 1977; 15: 73-8.
16. Smith JC, Peck JE, Ray LI, Smith EC. Aortoarteritis and sensorineural hearing loss in an adolescent black male. *Am J Otolaryngol* 2004; 25: 370-6.
17. Hall S, Barr W, Lie JT, Stanson AW, Kazmier FJ, Hunder GG. Takayasu arteritis: A study of 32 North American patients. *Medicine (Baltimore)* 1985; 64: 89-99.
18. Heggtveit HA. Nonatherosclerotic disease of the aorta. In: Silver MD, ed. *Cardiovascular pathology*. New York: Churchill Livingstone, 1983; 707-37.
19. Sen PK, Kinare SG, Kulkarni TP, Parulkar GB. Stenosing aortitis of unknown etiology. *Surgery* 1962; 51: 317-25.
20. Aggarwal A, Chag M, Sinha N, Naik S. Takayasu's arteritis: Role of mycobacterium tuberculosis and its 65 kDa heat shock protein. *Int J Cardiol* 1996; 55: 49-55.
21. Kumar Chauhan S, Kumar Tripathy N, Sinha N, Singh M, Nityanand S. Cellular and humoral immune responses to mycobacterial heat shock protein-65 and its human homologue in Takayasu's arteritis. *Clin Exp Immunol* 2004; 138: 547-53.
22. Muranjan MN, Bavdekar SB, More V, Deshmukh H, Tripathi M, Vaswani R. Study of Takayasu's arteritis in children: Clinical profile and management. *J Postgrad Med* 2000; 46: 3-8.
23. Kerr GS. Takayasu's arteritis. *Rheum Dis Clin North Am* 1995; 21: 1041-58.
24. Tripathy NK, Upadhyaya S, Sinha N, Nityanand S. Complement and cell mediated cytotoxicity by antiendothelial cell antibodies in Takayasu's arteritis. *J Rheumatol* 2001; 28: 805-8.
25. Tripathy NK, Sinha N, Nityanand S. Anti-annexin V antibodies in Takayasu's arteritis: Prevalence and relationship with disease activity. *Clin Exp Immunol* 2003; 134: 360-4.
26. Dhingra R, Talwar KK, Chopra P, Kumar R. An enzyme linked immunosorbent assay for detection of anti-aorta antibodies in Takayasu arteritis patients. *Int J Cardiol* 1993; 40: 237-42.
27. Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum* 1990; 33: 1129-34.
28. Moriwaki R, Noda M, Yajima M, et al. Clinical manifestations of Takayasu arteritis in India and Japan—new classification of angiographic findings. *Angiology* 1997; 48: 369-79.
29. Paul JF, Fiessinger JN, Sapoval M, et al. Follow-up electron beam CT for the management of early phase Takayasu arteritis. *J Comput Assist Tomogr* 2001; 25: 924-31.
30. Halefoglu AM, Yakut S. Role of magnetic resonance imaging in the early diagnosis of Takayasu arteritis. *Australas Radiol* 2005; 49: 377-81.
31. Uthman IW, Bizri AR, Hajj Ali RA, Nasr FW, Khalil IM. Takayasu's arteritis presenting as fever of unknown origin: Report of two cases and literature review. *Semin Arthritis Rheum* 1999; 28: 280-5.
32. Malik IS, Harare O, AL-Nahhas A, Beatt K, Mason J. Takayasu's arteritis: Management of left main stem stenosis. *Heart* 2003; 89: e9.
33. Park SH, Chung JW, Lee JW, Han MH, Park JH. Carotid artery involvement in Takayasu's arteritis: Evaluation of the activity by ultrasonography. *J Ultrasound Med* 2001; 20: 371-8.
34. Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for Takayasu arteritis. *Int J Cardiol* 1996; 54 (suppl): S141-7.
35. Lee HY, Rao PS. Percutaneous transluminal coronary angioplasty in Takayasu's arteritis. *Am Heart J* 1996; 132: 1084-6.
36. Matsubara O, Kuwata T, Nemoto T, Kasuga T, Numano F. Coronary artery lesions in Takayasu arteritis: Pathological considerations. *Heart Vessels Suppl* 1992; 7: 26-31.
37. Cipriano PR, Silverman JF, Perlroth MG, Griepp RB, Wexler L. Coronary arterial narrowing in Takayasu's aortitis. *Am J Cardiol* 1977; 39: 744-50.