Takayasu's arteritis

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Takayasu's arteritis, an inflammatory and obliterative disease of medium and large arteries, is classified as a giant cell arteritis. It has a predilection for the aortic arch and its branches and the pulmonary arteries. Unlike atherosclerotic vascular diseases, Takayasu's arteritis affects young women primarily. Early symptoms may be mainly systemic and may resemble polymyalgia rheumatica. The etiology is unknown, but infectious agents and autoimmunity have been suggested to play a role. Diagnosis is based on symptoms, physical findings, and angiographic findings, because tissue diagnosis rarely is feasible. The two cases reported here represent contrasting phases of Takayasu's arteritis.

Takayasu's arteritis is a relatively rare form of large vessel vasculitis. The ocular changes were described in 1908 by Takayasu,¹ and clinical findings were reported in 1948 by Shimizu and Sano.² Other names applied to this entity include pulseless disease, aortic arch syndrome, and idiopathic medial aortopathy and arteropathy.

Once thought to be limited to the aortic arch and its branches, the disease has been identified in the descending and abdominal aorta and in the renal arteries, with or without arch involvement.³ There is a female-to-male ratio of 8:1, with a predilection for young women. Although most cases have been reported from the Orient, increasing numbers have come from Europe⁴ and North America.^{3,4,5,6}

In the two cases reported here, the first patient presented with features of the early pulseless phase of the disease. The second case demonstrated some of the problems of evaluating the efficacy of therapy, especially in the late pulseless phase.

Report of cases

Case 1

A 37-year-old, black woman presented in January 1981 with mild effort claudication in the left arm, general fatigue, and upper extremity myalgia. No other limb claudication or Raynaud's phenomenon was present, and the patient denied arthralgias, syncope, headaches, fever, chest pain, or dizziness. There was no history of diabetes mellitus, hypertension, or tobacco use, and there

was no family history of premature atherosclerosis.

The patient's blood pressure was 130/64 mm Hg in the right arm and 110/76 mm Hg in the left arm. There were no bruits, pulse deficits, or murmurs, and no rashes or arthritis were present. The remainder of the physical examination had normal findings.

Laboratory evaluation revealed a hematocrit value of 42%, a white blood cell count of 8900/cu mm, and a Westergren sedimentation rate of 110 mm/h. Results of the VDRL test and tests for antinuclear antibody, rheumatoid factor, and cryoglobulins were negative. Serum complement levels and serum protein electrophoresis results were normal.

The chest film was normal, and an echocardiogram showed only a small pericardial effusion. An angiographic study of the aortic arch and its branches was remarkable for bilateral subclavian and axillary stenoses (Figs 1 and 2). Fluoroscopic examination showed the superior mesenteric, renal, and iliac arteries to be normal.

Takayasu's arteritis was diagnosed, and 60 mg of prednisone per day was prescribed. Within eight months, the symptoms decreased and the sedimentation rate normalized. The steroids were tapered and discontinued over the next two years; however, the blood pressure discrepancy in the arms remained unchanged.

In the subsequent 30 months, recurrent arm pain, right-sided numbness, and episodic transient visual blurring prompted reinstitution of steroid therapy at previous doses, as well as initiation of treatment with azathioprine (150 mg/d). The patient's physical findings remained unchanged, and multiple laboratory values, including sedimentation rates, were normal. Repeat chest film, electrocardiogram, and echocardiogram were normal, and an electromyographic-nerve conduction velocity study revealed minimal myopathic changes, which were thought to be compatible with steroid use. Two angiographic studies in May 1984 and March 1985 showed no changes from the original study.

It was not thought that active arteritis was present, and the azathioprine and prednisone were tapered and then discontinued. The patient subsequently has done well with avoidance of excessive upper extremity use, any there have been no new symptoms.

Case 2

A 32-year-old, black woman presented in February 1985 with a one-year history of progressively sharp substernal chest pain, left-sided facial and arm numbness, noneffort related left arm pain, and postural dizziness. There was no history of headaches, arthralgias, weight loss, fever, night sweats, weakness, jaw claudication, or syncope. The patient's past history was remarkable for four years of mild, untreated hypertension, three years of dia-

Figs 1 and 2. Angiographic views of right (Fig 1) and left (Fig 2) subclavian and axillary arteries (case 1). A smooth-walled, tapered narrowing of 10 cm is present along the right axillary artery, and a 5-cm narrowing is present along the left subclavian artery.

betes mellitus treated intermittently with insulin, and eight pack-years of cigarette smoking. There was no premature atherosclerosis in her family.

The patient's temperature was 98.4°F; the blood pressure was 100/70 mm Hg in the right arm and 140/84 mm Hg in the left arm. The right radial pulse was weaker than the left, and there was a grade III/VI holosystolic murmur, which was best heard in the aortic area. There were prominent bruits over the carotid arteries and supraclavicular areas, but no neurologic deficits were elicited. The rest of the physical examination had normal results.

Laboratory studies revealed a hematocrit value of 36.4%, a white blood cell count of 10,300/cu mm, and a Westergren sedimentation rate of 29 mm/h. The fasting blood sugar level was 150 mg/dL, and the cholesterol value was 281 mg/dL. The VDRL and tests for antinuclear antibody and rheumatoid factor were negative. A purified protein derivative (PPD) test was nonreactive, with a positive mumps control.

An echocardiogram showed mild left ventricular hypertrophy, and a 24-hour Holter monitor revealed intermittent sinus tachycardia. An exercise treadmill test and computed tomographic scan of the head were normal. Carotid ultrasonography suggested a large plaque at the left carotid bifurcation and 70% to 80% stenosis of the right internal carotid artery. Angiographic examination revealed multiple stenoses involving the left carotid bifur-

cation (Fig 3), innominate artery (Fig 4), right internal carotid artery, and origin of the left vertebral artery.

Based on the size of the involved vessels and the short duration of fairly mild diabetes, the vascular disease was diagnosed as Takayasu's arteritis rather than diabetic atherosclerosis. Prednisone therapy (60 mg/d) was begun; additional daily medications included 80 mg of aspirin and 150 mg of dipyridamole. There was no significant change in the patient's symptoms, but she developed frank diabetes, which required insulin, and glaucoma, which required timolol in drops.

Two months after discharge, the patient was hospitalized again for severe chest pain, and an acute myocardial infarction was confirmed. Coronary angiography revealed 99% mid-right coronary, 50% proximal left anterior descending, and 50% proximal left circumflex occlusions. There was slight mild inferior and septal akinesis. Medical treatment was suggested, and the angina has been controlled with nitrates. Prednisone has been tapered gradually without new symptoms or physical findings or neurologic deterioration. Sedimentation rates have been in the range of 10 to 15 mm/h.

Discussion

Takayasu's arteritis has been defined as a nonspecific, inflammatory, obliterative disease of large and medium arteries and has been classified as giant cell arteritis.⁴ The early histologic changes resemble a granulomatous inflammation, with mononuclear, polymorphonuclear, and multinucleated giant cell infiltration of the adventitia. Inflammatory and thrombotic changes occur in the vasa vasorum, and there are secondary changes in the media. With progression, the granulomas become fibrotic, with collagen deposition in the adventitia and degeneration of the media.

Figs 3 and 4. Angiographic views of the left carotid bifurcation (Fig 3) and the innominate artery (Fig 4). Focal tight stenoses are present.

Narrowing of an involved segment is produced by both initial smooth muscle proliferation and fibrosis and by contraction of the fibrotic adventitia and media, which produces thrombosis and aneurysm formation. The morphologic expression of Takayasu's arteritis closely resembles the large vessel disease of temporal arteritis and the seronegative spondyloarthropathies.

Based on the distribution of the lesions, four patterns of Takayasu's arteritis have been described. There is involvement of the aortic arch and its branches, lesions in the descending and abdominal aorta and renal arteries, and a combination of these. Pulmonary artery involvement with other large vessel disease also has been reported.^{5,7}

The etiology is obscure. Elevated antistreptolysin O and C reactive protein titers in some patients have suggested group A *Streptococcus* as a causative agent.⁴ PPD positivity in as many as 80% of patients, along with giant cell granulomas, has suggested a relationship with tuberculosis.⁶ In addition, skin reactions with specific antigens of *Mycobacterium kansasii* and *M avium* have been reported to be positive more often in Takayasu's ar-

teritis patients than in the average population.⁷

Changes similar but not identical to the lesions of Takayasu's arteritis can be produced after the inoculation of *M tuberculosis* into the subadventitial layer of the rabbit carotid artery⁸; however, the bacteria never have been demonstrated in any arterial histologic sections, and it may be that antigenic fractions of various mycobacteria may cause a toxic injury to the vessel wall.

Consensus opinion favors an autoimmune etiology because of frequently increased gammaglobulin levels, sporadic false-positive VDRL results, and positive rheumatoid factors and antinuclear antibodies tests. The presence of antiarterial antibodies has been found in one study,⁹ but other researchers¹⁰ failed to confirm this finding. A genetic predisposition has been suggested because of a reported increased association of HLA-BW52 and Takayasu's arteritis.⁴

Symptoms may relate directly to vascular occlusion and insufficiency or to systemic manifestations. In the prepulseless or early pulseless phases, constitutional symptoms, such as fever, fatigue, dyspnea, weight loss, and anorexia, or polymyalgia-type symptoms, such as arthralgias, myalgias, and stiffness may predominate, with the difference being the presentation in younger people in Takayasu's arteritis.

In addition, signs of local circulatory deficit, such as limb claudication (present in case 1), Raynaud's phenomenon, hypertension, or angina may occur. Tenderness of the main arterial trunks and arterial bruits may be present. This presentation is seen in about half of all cases; it may be intermit-

tent throughout the disease course, or it may merge with a late pulseless phase, during which symptoms generally are related to the location of the lesions, as in case 2.

Some patients have advanced arterial obstruction when they first develop symptoms. They present with prominent cardiovascular and neurologic manifestations, such as aortic or mitral valvular insufficiency, congestive heart failure, pulmonary hypertension, headaches, seizures, or frank hemiplegia. Early or late systemic hypertension is found in 50% to 60% of patients; it is due to renovascular mechanisms in a majority of patients.⁷

Similar to those seen in temporal arteritis, ocular symptoms, including blurring and even visual loss, can occur at any time in the disease course, but they are uncommon. Gastrointestinal symptoms and signs are rare. Collateral circulation in this area is extensive and may ameliorate any symptoms. Syncope, which is quite common, likely is secondary to decreased cerebral blood flow rather than to baroreceptor hypersensitivity.¹¹

Useful laboratory data are scarce. Mild leukocytosis and normochromic, normocytic anemia may be present. The Westergren sedimentation rate is the most useful tool for gauging disease activity during the prepulseless and early pulseless phase. It is elevated early, usually to >50 mm/h, in 70% to 100% of cases. However, the sedimentation rate tends to decrease with time, especially during the late pulseless phase.

Because tissue diagnosis is rarely available or practical without significant morbidity prior to actual resection or bypass surgery, angiography is the most useful diagnostic study. Vascular segments with smooth-walled, tapered, focal or prolonged narrowing with other areas of dilation may be seen.¹² However, repeated angiography may injure the vascular endothelium, thus increasing the risk of thrombosis and occlusion, and follow-up studies should be reserved for patients with significant new symptoms or physical findings.

Differential diagnosis of the vascular occlusions includes traumatic narrowing, atherosclerosis, congenital lesions, and pulmonary emboli. In diabetic patients, macrovascular disease can occur; however, the degree of atherosclerosis correlates best with the longer duration of disease and the advancing age of the patient.¹³ Ultrasonography may prove to be a useful screening and follow-up study.

Various therapeutic measures, including corticosteroids, immunosuppressives, vasodilators, anticoagulants, nonsteroidal anti-inflammatory drugs, and antiplatelet agents, have been tried. Treatment with corticosteroids in the acute phase

seems to be beneficial; however, after fibrous tissue has been deposited and thrombosis has occurred, the response is diminished, and the benefits of treatment must be weighed against the potential risks.

One report¹⁴ suggests that 30 mg/d of prednisone for two to three months, followed by gradual tapering to a maintenance dose, is effective. Consensus favors 50 to 60 mg/d initially, with dosage reductions based on symptomatic improvement and a falling sedimentation rate. Therapy with cyclophosphamide in some patients who had clinical or angiographic progression when taking only prednisone has been reported to be effective.¹⁵

When medical treatment to control severe hypertension or vascular insufficiency has failed, surgical procedures, including resection, bypass, and endarterectomy, may be necessary. Surgery preferably should be performed during the chronic or late pulseless phase, for fear of occlusions of new grafts or breakdown at anastomotic sites.⁷

Prognosis should be assessed on the basis of extent, location, and complications of the vasculitis. Some spontaneous remissions have been reported, but these cases are unusual. Death has occurred, most commonly as a result of congestive heart failure or cerebrovascular accidents; aneurysmal rupture is uncommon. Two follow-up studies have demonstrated five-year survival rates of 85%¹⁶ and 94%.¹⁷ Survival rate statistics beyond five years are not available.

Summary

Takayasu's arteritis, a large artery vasculitis of unknown etiology, primarily affects young women. Symptoms may be systemic primarily or may be secondary to major organ vascular insufficiency. It is important to recognize that symptoms in the prepulseless or early pulseless phase may resemble polymyalgia rheumatica, with only minimal evidence of vascular compromise, and that the only laboratory abnormality may be an elevated sedimentation rate. Patients should be evaluated carefully for pulse deficits, blood pressure differences in the extremities, or bruits, because response to treatment with corticosteroids or immunosuppressive agents is most effective during these stages.

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