Takayasu
Clinical Features and Diagnosis of Takayasu arteritis

CPC on 12 Sept 07
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INTRODUCTION

- Takayasu arteritis is a chronic vasculitis of unknown etiology.
- Women are affected in 80 to 90 percent of cases, with an age of onset that is usually between 10 and 40 years.
- It has a worldwide distribution, with the greatest prevalence in Asians. In Japan, it has been estimated that 150 new cases occur each year.
- HLA-Bw52 and HLA-B39.2 have been increased in frequency in several studies, suggesting an immunogenetic association.
INTRODUCTION

- Takayasu arteritis primarily affects the aorta and its primary branches [8].
- The inflammation may be localized to a portion of the thoracic or abdominal aorta and branches, or may involve the entire vessel.
- The initial vascular lesions frequently occur in the left middle or proximal subclavian artery.
- The abdominal aorta and pulmonary arteries are involved in approximately 50 percent of patients.
INTRODUCTION

- The inflammatory processes cause thickening of the walls of the affected arteries.
- The proximal aorta may become dilated secondary to inflammatory injury.
- Narrowing, occlusion, or dilation of involved portions of the arteries in varying degrees results in a wide variety of symptoms.
PATHOGENESIS

- The pathogenesis of Takayasu arteritis is poorly understood.
- Cell-mediated mechanisms are thought to be of primary importance and may be similar to those in giant cell (temporal) arteritis.
Pathology

- Active inflammation is indicated by the presence of mononuclear cells, predominantly lymphocytes, histiocytes, macrophages, and plasma cells.
- Giant cells and granulomatous inflammation are typically found in the media.
- Destruction of the elastic lamina and the muscular media can lead to aneurysmal dilation of the affected vessel.
Pathology

- Alternatively, progressive inflammation and dense scarring may proceed from the adventitia leading to a compromise of the vascular lumen.

- Intimal proliferation may also contribute to the development of stenotic arterial lesions.

- If active inflammation abates, dense scar tissue remains as an indication of prior vasculitis.
Immunopathogenesis

- Immunohistopathologic examination has shown that the infiltrating cells in aortic tissue mainly consist of killer cells, especially gamma delta T lymphocytes.
- In another report, the T cell receptors on the infiltrating T cells had a restricted repertoire, suggesting that a specific but as yet unidentified antigen in aortic tissue might be targeted. This change was not seen in atherosclerotic aortic aneurysms.
Immunopathogenesis

- In one study of 19 patients, antiendothelial antibodies were found in 18, and the titers were approximately 20 times greater than normal.
- No patient had autoantibodies associated with other forms of vascular injury such as antinuclear, antineutrophil cytoplasmic, anti-DNA, or antiphospholipid antibodies.
CLINICAL MANIFESTATIONS

Symptoms

- Constitutional symptoms
  - Early phase of Takayasu arteritis caused by the systemic effects of cytokines, particularly interleukin-6, includes fatigue, weight loss, and low-grade fever.

- Vascular symptoms as disease progressed
  - The evidence of vascular involvement and insufficiency becomes clinically apparent due to dilation, narrowing, or occlusion of the proximal or distal branches of the aorta. The extremities become cool, and pain develops with use (arm or leg claudication).
CLINICAL MANIFESTATIONS

Other symptoms

- **Arthralgias or myalgias** occur in about one-half of cases may be confused with those of juvenile rheumatoid arthritis early in the course.

- **Skin lesions resembling erythema nodosum or pyoderma gangrenosum** are found over the legs in a minority of cases. The lesions frequently show vasculitis of small vessels on biopsy.

- **The pulmonary arteries are involved pathologically in up to 50 percent of cases.** Pulmonary manifestations include chest pain, dyspnea, hemoptysis, and pulmonary hypertension. Complaints of dyspnea may also be due to heart failure resulting from aortic dilation and aortic regurgitation.
Symptoms

- **Vascular symptoms as disease progressed**
  - Involvement of the carotid and vertebral arteries lead to vertigo, syncope, orthostasis, headaches, convulsions, and dementia and visual impairment.
  - Abdominal pain, diarrhea, and gastrointestinal hemorrhage may result from mesenteric artery ischemia.
  - Angina pectoris occurs due to coronary artery. Myocardial infarction may occur.
  - Aortic regurgitation that is due initially to marked dilatation of the ascending aorta; the regurgitant jet may then induce secondary injury to the aortic valve.
CLINICAL MANIFESTATIONS

Physical examination

- Fever
- Reduced blood pressure in one or both arms is common; a differential of more than 10 mmHg between the arms is typically present.
- Arterial pulses in the arms and legs are diminished and often asymmetrical. Bruits are usually audible over the involved vascular sites.
- Synovitis may be palpable early in the disease over larger joints such as the knees or wrists.
- Hypertension develops in more than one-half of cases due to narrowing of the renal artery, or narrowing and decreased elasticity of the aorta and branches.
CLINICAL MANIFESTATIONS

Laboratory findings

- CBC, a normochromic normocytic anemia, suggest the anemia of chronic disease. The white blood cell count is usually normal.

- Acute phase reactants, such as an elevated ESR, increased serum C-reactive protein and alpha-2 globulin concentrations, and hypoalbuminemia, are a reflection of the underlying inflammatory process. These tests are not always precise or invariably reliable indicators, but usually reflect the activity state of the disease.

- Autoantibodies associated with other forms of vascular disease, including antinuclear, antineutrophil cytoplasmic, anti-DNA, and antiphospholipid antibodies, are not found in Takayasu arteritis.
Imaging studies

- Chest X-ray may reveal dilation of the aorta or increased mediastinal widening suggesting aneurysmal dilation of the great vessels.

- Arteriography.
  - The primarily abnormalities are smooth-walled, tapered, focal, or narrowed areas with some areas of dilation.
  - It may define the location and appearance of the arterial lesion, and may also allow a therapeutic intervention (e.g., angioplasty and/or stenting of a stenotic area).
  - It is an invasive test associated with some risks. Therefore, if a therapeutic intervention is not anticipated, a less invasive imaging technique may be preferred.
CLINICAL MANIFESTATIONS

Imaging studies

- CT and MRI — Computed tomographic (CT) or magnetic resonance (MR) imaging scans of the chest, abdomen, head and neck, or other areas are helpful in evaluating large arteries.

- CT angiography was 95 percent sensitive and 100 percent specific for the diagnosis of Takayasu arteritis, and was more sensitive than conventional angiography in detecting mural vessel changes.
CLINICAL MANIFESTATIONS

Imaging studies

- Ultrasonography
  - Transthoracic ultrasound examinations may help detect alterations in the aorta and its branches, particularly the ascending thoracic aorta.
  - Transesophageal ultrasound provides a better view of the descending aorta.
CLINICAL MANIFESTATIONS

Imaging studies

- Positron emission tomography
  - Positron emission tomography (PET scanning) utilizing radioactively labeled fluorodeoxyglucose can be used to image the aorta and great vessels.
  - Areas of increased uptake of the tracer correlate well with abnormal arterial segments noted by MRI.
  - Uptake does correlate with other clinical markers of inflammation.
  - The use of PET scanning for the diagnosis and/or management of patients with suspected or established Takayasu arteritis requires further investigation.
The American College of Rheumatology Classification Criteria

At least three of the six criteria are present yields a sensitivity and specificity of 90.5 and 97.8 percent, respectively

- Age at disease onset 40 years
- Claudication of the extremities
- Decreased pulsation of one or both brachial arteries
- Difference of at least 10 mmHg in systolic blood pressure between the arms
- Bruit over one or both subclavian arteries or the abdominal aorta
- 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, fibromuscular dysplasia, or other causes.
American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis

<table>
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<tr>
<th>Criterion</th>
<th>Definition</th>
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<tr>
<td>Age at disease onset ≤ 40 years</td>
<td>Development of symptoms or findings related to Takayasu arteritis at age ≤ 40 years</td>
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<tr>
<td>Claudication of extremities</td>
<td>Development and worsening of fatigue and discomfort in muscles of one or more extremities while in use, especially the upper extremities</td>
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<tr>
<td>Decreased brachial artery pressure</td>
<td>Decreased pulsation of one or both brachial arteries</td>
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<tr>
<td>Blood pressure difference &gt; 10 mmHg</td>
<td>Difference of &gt;10 mmHg in systolic blood pressure between arms</td>
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<tr>
<td>Bruit over subclavian arteries or aorta</td>
<td>Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta</td>
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<tr>
<td>Arteriogram abnormality</td>
<td>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, fibromuscular dysplasia, or similar causes; changes usually foci or segmental</td>
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For purposes of classification, a patient shall be said to have Takayasu 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 percent and a specificity of 97.8 percent.

The early diagnosis of Takayasu arteritis may be difficult since early symptoms such as fatigue, malaise, joint aches, and low-grade fever are nonspecific.

However, differences in blood pressure between the arms, or bruits over the neck, supraclavicular areas, axillae, or abdomen are the suspicious signs.
Differential Diagnosis

Several disorders, including many forms of vasculitis, must be distinguished from Takayasu arteritis.

- **Fibromuscular dysplasia** — Fibromuscular dysplasia is usually more focal in its involvement and is not associated with the systemic symptoms of Takayasu arteritis.

- **Ergotamine** — Excess ergotamine intake may cause reversible spasm of the large blood vessels and mimic some of the clinical findings.

- **Ehlers-Danlos syndrome** — Ehlers-Danlos syndrome may be associated with vascular abnormalities, particularly multiple aneurysms, which may rupture and cause diagnostic confusion; once again the systemic signs of inflammation are absent.
Differential Diagnosis

- Giant cell (temporal) arteritis — Perhaps the most difficult distinction is between Takayasu arteritis and giant cell (temporal) arteritis. Both involve large arteries which show granulomatous vasculitis on histologic examination. Both respond to corticosteroids. Distinction between the two disorders can usually be made based upon the age of the patient and the distribution of lesions.
## Distinguishing features of giant cell versus Takayasu arteritis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Giant cell arteritis</th>
<th>Takayasu arteritis</th>
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<tbody>
<tr>
<td>Female-to-male ratio</td>
<td>3:2</td>
<td>7:1</td>
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<tr>
<td>Age at onset</td>
<td>&gt;50 years</td>
<td>&lt;40 years</td>
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<tr>
<td>Ethnic ancestry</td>
<td>European</td>
<td>Asian</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Granulomatous inflammation</td>
<td>Granulomatous inflammation</td>
</tr>
<tr>
<td>Primary vessels involved</td>
<td>External carotid artery branches</td>
<td>Aorta and branches</td>
</tr>
<tr>
<td>Renovascular hypertension</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>HLA association</td>
<td>HLA-DR4</td>
<td>HLA-Bw52</td>
</tr>
<tr>
<td>Course</td>
<td>Self-limited</td>
<td>Chronic</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td>Surgical intervention needed</td>
<td>Rare</td>
<td>Common</td>
</tr>
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Diagnosis summary and recommendations

- The presence of constitutional symptoms such as fever, malaise, weight loss, myalgias and ischemic symptoms or signs of one or more large arterial stenoses should raise a suspicion for Takayasu arteritis when these features occur in someone younger than 40 years.

- Testing for acute phase reactants such as the ESR and CRP may provide additional support for the presence of an inflammatory disorder.

- The diagnosis is seldom made histologically.

- In most cases the diagnosis is based upon suggestive clinical features and imaging of the arterial tree by MRI, CT, or angiography.
The mainstay of therapy for Takayasu arteritis is glucocorticoids. Angioplasty or bypass grafts may be necessary once irreversible arterial stenosis has occurred. Treatment of hypertension and heart failure should be instituted if these complications occur.
Glucocorticoids effectively suppress the systemic symptoms and usually arrest progression of Takayasu arteritis. The normochromic anemia and elevated acute phase reactants also return to normal.

Arterial stenosis may reverse and ischemic symptoms may improve in early cases. However, the vascular response is diminished once fibrous tissue has formed in the involved vessels or thrombosis has occurred.
TREATMENT

- Initial glucocorticoid dose 45 to 60 mg of prednisone or its equivalent dose should be started in an adult of average size.

- Assessing response to treatment. A decrease and eventual disappearance of constitutional symptoms is expected and is typically accompanied by a decrease in acute phase reactants such as ESR and CRP levels.
TREATMENT

- CT or MRI scans can also be used to follow the response to treatment.
- The potential efficacy of this approach was evaluated in 31 patients in whom repeat CT angiography was performed over a median period of three years.
- Thoracic or abdominal aortic aneurysms were initially noted in 12 patients (approximately 40 percent) and subsequently developed in 2 during follow-up. Rapidly increasing aneurysmal size (more than 1 cm/year) occurred in three patients despite glucocorticoid therapy; this was accompanied by mural thickening (suggestive of continued disease activity), eventually culminating in aortic rupture.
TREATMENT

- Prevent glucocorticoid-induced bone mineral loss
- Supplementation with calcium and vitamin D are recommended.
- Prophylactic use of an oral bisphosphonate (e.g., alendronate or risedronate) can be initiated while awaiting results of an initial study of bone mineral density. If osteoporosis is present, full-dose regimens rather than prophylactic treatment is warranted.
TREATMENT

- MECHANISM OF ACTION — A bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; decreases the rate of bone resorption, leading to an indirect increase in bone mineral density. In Paget's disease, characterized by disordered resorption and formation of bone, inhibition of resorption leads to an indirect decrease in bone formation; but the newly-formed bone has a more normal architecture.
TREATMENT

Glucocorticoid resistant disease

- Approximately one-half of all patients with Takayasu arteritis have chronic active disease for which glucocorticoid therapy alone does not provide sustained remissions.
  - Methotrexate,
  - Azathioprine
TREATMENT

- Glucocorticoid resistant disease (cont)
  - Anti-TNF agents
  - Other medications:
    - Cyclophosphamide: mycophenolate mofetil, leflunomide.
PROGNOSIS

- Takayasu arteritis is a chronic disease. The degree of activity over time varies, with apparent exacerbations and reductions or remissions in the intensity of the inflammatory processes. The disease may eventually burn out.
PROGNOSIS

- One study investigating prognostic factors associated with this disease found two major predictors of outcome:
  - the incidence of complications (Takayasu's retinopathy, hypertension, aortic regurgitation, and aneurysm);
  - the presence of a progressive course.
The 15-year survival was 66 versus 96 percent for patients with and without a major complication, and 68 versus 93 percent for those with and without a progressive course.

The presence of both a major complication and progressive course was the worst prognostic indicator (43 percent survival at 15 years). In contrast, no patient died who had neither of these manifestations. These variables may identify a subset of patients who require more aggressive medical and/or surgical therapy.
The long-term prognosis among patients who required surgical revascularization was addressed in a study of 106 such Japanese patients and followed for a mean of 19.8 years. Survival to hospital discharge was 89 percent; overall survival at 20 years was 73.5 percent. Anastomotic aneurysms developed in 13.8 percent of long-term survivors at various times following surgery. Life-long surveillance for the development of this complication has been recommended by authors at one center.