

# Thromboangiitis Obliterans (Buerger's disease)

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## Abstract

*Thromboangiitis obliterans or Buerger's disease is a segmental occlusive inflammatory condition of arteries and veins, with thrombosis and recanalization of the affected vessels. It is a nonatherosclerotic inflammatory disease affecting small and medium sized arteries and veins of upper and lower extremities. The clinical criteria edited by Olin in 2000 include: age under 45 years; current or recent history of tobacco use; presence of distal-extremity ischemia, indicated by claudication, pain at rest, ischemic ulcers or gangrenes, and documented by non-invasive vascular testing; exclusion of autoimmune diseases, hypercoagulable states and diabetes mellitus; exclusion of a proximal source of emboli by echocardiography or arteriography; consistent arteriographic findings in the clinically involved and non-involved limbs. The disease is found worldwide, the prevalence among all patients with peripheral arterial disease ranges from values as low as 0.5 to 5.6% in Western Europe to values as high as 45 to 63% in India, 16 to 66% in Korea and Japan, and 80% among Jews of Ashkenazi. The etiology of thromboangiitis obliterans is unknown, but use or exposure to tobacco is central to the initiation and progression of the disease. If the patient smokes, stopping completely is an essential first step of treatment. The role of other treatments including vasodilating or anti-clotting drugs, surgical revascularization or sympathectomy in preventing amputation or treating pain, remains unclear.*

## Key-words

Thromboangiitis obliterans, Buerger's disease, peripheral ischemia, infrapopliteal arterial occlusions, tobacco use.

## Disease name and synonyms

Thromboangiitis obliterans

Buerger's disease

veins, with thrombosis and recanalization of the affected vessels [1,2]. It is a nonatherosclerotic inflammatory disease affecting small and medium sized arteries and veins of upper and lower extremities [3].

## Definition

Thromboangiitis obliterans (TAO) is a segmental occlusive inflammatory condition of arteries and

## Diagnostic criteria

Since specificity of Buerger's disease is characterized by peripheral ischemia of an inflammatory nature and with a self-limiting course, diagnostic criteria should be discussed from clinical point of view.

Several different criteria have been proposed for the diagnosis of thromboangiitis obliterans.

### **Diagnostic criteria of Shionoya (1998) [4]:**

- smoking history;
- onset before the age of 50 years;
- infrapopliteal arterial occlusions;
- either arm involvement or phlebitis migrans;
- absence of atherosclerotic risk factors other than smoking.

### **Diagnostic criteria of Olin (2000) [5]:**

- age under 45 years;
- current or recent history of tobacco use;
- the presence of distal-extremity ischemia, indicated by claudication, pain at rest, ischemic ulcers or gangrenes, and documented by non-invasive vascular testing;
- exclusion of autoimmune diseases, hypercoagulable states and diabetes mellitus;
- exclusion of a proximal source of emboli by echocardiography or arteriography;
- consistent arteriographic findings in the clinically involved and non-involved limbs.

## Differential diagnosis

The distal nature of thromboangiitis obliterans and the involvement of the legs and arms help to differentiate it from atherosclerosis. Internal elastic lamina and the media are preserved in patients with thromboangiitis obliterans, contrarily to systemic vasculitis, in which disruption of these lamina is usually striking [6].

An abnormal Allen test result [7,8] in a young smoker presenting with leg ulcerations is highly suggestive of thromboangiitis obliterans; this test demonstrates small vessel involvement in both the arms and the legs. However, an abnormal result can also be present in other types of small vessel occlusive disease of the hand such as [scleroderma](#), CREST syndrome (calcinosis cutis, Raynaud phenomenon, sclerodactyly, and telangiectasia), repetitive trauma, emboli, hypercoagulable states and vasculitis.

## Epidemiology

The disease is found worldwide, but the highest incidence of thromboangiitis obliterans occurs in the Middle East and Far East [9,10]. The prevalence of the disease in the general population in Japan was estimated at 5/100,000 persons in 1985 [11]. The prevalence of the disease among all patients with peripheral

arterial disease ranges from values as low as 0.5 to 5.6% in Western Europe to values as high as 45 to 63% in India, 16 to 66% in Korea and Japan, and 80% among Jews of Ashkenazi ancestry living in Israel. Part of this difference in disease incidence may be due to variability in diagnostic criteria [12,13].

## Clinical description

The onset of Buerger's disease occurs between 40 and 45 years of age, and men are most commonly affected. It begins with ischemia of the distal small vessels of the arms, legs, hands and feet. Involvement of the large arteries is unusual and rarely occurs in the absence of small-vessel occlusive disease [14]. Patients may present with claudication of the feet, legs, hands, and arms. The pain typically begins in the extremities but may radiate to more central parts of the body. As the disease progresses, typical calf claudication and eventually ischemic pain at rest and ischemic ulcerations on the toes, feet, or fingers may develop [5]. Because of the likelihood of involvement of more than one limb [15], it is advisable to obtain an arteriogram of both arms, either legs, or all four limbs in patients who present with clinical involvement of only one limb. Limbs not clinically affected could present arteriographic abnormalities. Other signs and symptoms of disease may include numbness and/or tingling in the limbs, skin ulcerations and gangrene of the digits. Superficial thrombophlebitis and Raynaud's phenomenon occurs in approximately 40% of patients with thromboangiitis obliterans [3].

Although Buerger's disease most commonly affects the small and medium-sized arteries and veins in the arms, hands, legs and feet, it has been reported in many other vascular beds. There are case reports of involvement of the cerebral and coronary arteries, aorta, intestinal vessels, and even multiple-organ involvement may exist [16-19].

When thromboangiitis obliterans occurs in unusual locations, the diagnosis should be made only when histopathological examination identifies the acute-phase lesions [3].

Gastrointestinal involvement of thromboangiitis obliterans remains rare, however, intestinal manifestations, like stricture or perforation of the colon, can precede long before symptoms of severe peripheral arterial disease in patients with thromboangiitis obliterans [18].

## Etiology

Although the cause of Buerger's disease is unknown, the strongest association is with tobacco use [3]. Use or exposure to tobacco is

central to the initiation and progression of the disease.

Adar *et al.* [20] showed by using an antigen-sensitive thymidine-incorporation assay, that patients with thromboangiitis obliterans have an increased cellular sensitivity to type I and III collagen compared to patients with arteriosclerosis obliterans or healthy male controls. De Moerloose *et al.* [21] found a marked decrease in frequency of the HLA-B12 antigen in patients with Buerger's disease (2.2% vs. 28% in controls). This disorder may, like other autoimmune diseases, have a genetic predisposition without a direct "cause" by a mutant gene. Most investigators feel that Buerger's disease is an immune-mediated endarteritis; recent immunocytochemical studies have identified the linear deposition of immunoglobulins and complement factors along the elastic lamina [22]. The inciting antigen has not been discovered. The role of hyperhomocysteinemia in the pathogenesis of Buerger's disease is controversial [23]. Some association between thrombophilic conditions such as antiphospholipid syndrome and Buerger's disease has also been suggested [24]. Peripheral endothelium-dependent vasodilation is impaired in patients with Buerger's disease while non-endothelial mechanisms of vasodilation seem to be intact [25].

### Histopathology

While the clinical criteria of TAO are relatively well defined, there is no consensus on histopathological findings [26]. It is especially difficult to distinguish TAO morphologically from arteriosclerosis obliterans (ASO). Histopathological findings are also known to vary according to the duration of the disease [3]. The findings are most likely to be diagnostic in the acute phase of the disease, most commonly when a segment of a vessel with superficial thrombophlebitis undergoes biopsy [5]. Other histopathological phases such as, intermediate (subacute) and end-state (chronic) phases have been described. The **acute-phase lesions** include an occlusive, highly cellular, inflammatory thrombus, with less inflammation in the walls of the blood vessels. Polymorphonuclear leukocytes, microabscesses and multinucleated giant cells may exist. When thromboangiitis obliterans occurs in unusual locations, the diagnosis should be made only when histopathological examination identifies the acute-phase lesion.

In the **intermediate phase** of disease there is progressive organization of the thrombus in the arteries and veins.

When only organized thrombus and fibrosis are found in the blood vessels, the phase is considered to be the **end-stage phase** [27-29].

### Diagnostic methods

No specific laboratory test to diagnose Buerger's disease is available. Unlike other types of vasculitis, the acute-phase reactions such as the erythrocyte sedimentation rate and C-reactive protein are normal in patients with Buerger's disease [3].

Recommended tests to rule out other causes of vasculitis include a complete blood cell count, liver function tests, serum creatinine determination, fasting blood sugar level, sedimentation rate, antinuclear antibody, rheumatoid factor, serologic markers for CREST syndrome and scleroderma, and screening for hypercoagulability. The screening for hypercoagulopathy including antiphospholipid antibodies and homocystein in patients with Buerger's disease is also recommended.

If a proximal source of embolization is suspected, transthoracic or transoesophageal echocardiography and arteriography should be performed. Angiographic findings include severe distal, segmental occlusive lesions but the more proximal arteries are normal. The role of modern imaging methods, such as computerised tomography, and magnetic resonance imaging in diagnosis and in differential diagnosis of Buerger's disease still remains unsettled. In patients with leg ulceration suspected of having thromboangiitis obliterans, the Allen test should be performed to assess the circulation in the hands and fingers [7].

### Management including treatment

The most effective treatment for Buerger's disease is smoking cessation. It is therefore essential that patients diagnosed with Buerger's disease stop smoking immediately and completely to prevent progression of the disease and avoid amputation [3,30]. Early treatment is also important, because Buerger's disease may provoke social problems that influence quality of life [31]. Even smoking one or two cigarettes/day or using smokeless tobacco (chewing tobacco or patch with nicotine) may keep the disease active [32,33]. If there is no gangrene when the patient discontinues smoking, amputation is avoided. Patients who continue smoking are generally the ones who require amputation of fingers and toes.

Physicians must educate and counsel their patients repeatedly about the importance of discontinuing the use of all tobacco products.

The correlation between smoking and disease is very strong, however patients continue to have claudication or Raynaud's phenomenon after stopping completely to use tobacco [3].

Supportive care should be directed towards maximizing blood supply including avoiding

vasoconstriction from exposure to cold or drugs. Care should be taken to avoid thermal, chemical, or mechanical injury, especially from poorly fitting footwear or minor surgery of digits, and fungal infection.

Despite the clear presence of inflammation in this disorder, anti-inflammatory agents such as steroids have not shown to be really beneficial. Intravenous iloprost therapy (a prostaglandin analogue) shows that this drug is superior to aspirin with total relief of pain at rest and complete healing of all trophic changes. It decreased the need for amputation [34]. Although acetylsalicylic acid is often prescribed to patients with Buerger's disease, no controlled studies to show benefit of this or other per oral anti-clotting agents are available. Intra-arterial thrombolytic therapy by streptokinase has been tested in some patients with gangrene or pre-gangrenous lesions of the toes or feet with some success in avoiding amputation [35].

Arterial revascularization is not usually possible for patients with thromboangiitis obliterans, because of the diffuse segmental involvement and distal nature of the disease [3]. The role of bypass to the distal arteries for patients with Buerger's disease remains also controversial, because of the high incidence of graft failure [36]. However, if the patient has severe ischemia and there is a distal target vessel, bypass surgery with the use of an autologous vein should be considered [37,38,39].

Sympathectomy decreases arterial spasm, which is the reason for assessing this procedure in patients with Buerger's disease. Laparoscopic method for sympathectomy has also been used [40,41]. Sympathectomy seems to provide short-term pain relief and promotes ulcer healing in some patients with Buerger's disease, but carries no long-term benefit [40]. Spinal cord stimulator and vascular endothelial growth factor gene therapy have been used experimentally in patients with Buerger's disease with promising results [42-43].

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