Thromboangiitis Obliterans
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Case presentation: A 39-year-old male smoker with a 2-year history of calf discomfort on ambulation culminating in left femoral-to-peroneal artery bypass presented with right leg discomfort and recurrent painful subcutaneous nodules on his feet and calves. Biopsy of a nodule from his right foot was interpreted as vasculitis with thrombosis and fibrinoid necrosis in subcutaneous vessels, and the patient was prescribed immunosuppressive therapy with prednisone and azathioprine. His symptoms progressed, and the patient referred himself to the vascular medicine clinic for a second opinion. On examination, the patient had tender erythematous nodules on his right foot and calf following the course of the right lesser saphenous vein consistent with extensive superficial thrombophlebitis. The right femoral, popliteal, and pedal pulses were palpable. The left femoral-to-peroneal graft and left pedal pulses were also palpable. Ankle:brachial indices were normal in each leg. The constellation of arterial occlusive disease and superficial thrombophlebitis in a young smoker was most consistent with thromboangiitis obliterans.

Overview
Thromboangiitis obliterans is a segmental nonatherosclerotic inflammatory disorder that involves primarily the small and medium arteries, veins, and nerves of the extremities. Von Winiwarter provided the first description of a patient with thromboangiitis obliterans in 1879. Thromboangiitis obliterans is also known as Buerger’s disease, named after Leo Buerger who published a detailed description of the pathological findings of amputated limbs in patients with the disease in 1908.

The annual incidence of thromboangiitis obliterans is reported to be 12.6 per 100,000 in the United States. Although it is observed worldwide, thromboangiitis obliterans is more prevalent in the Middle East and Far East. The disease typically presents in patients 45 years of age. Young men are more frequently affected, but thromboangiitis obliterans also occurs in women.

Pathophysiology
Thromboangiitis obliterans is a vasculitis characterized by a highly cellular inflammatory thrombus with relative sparing of the vessel wall. Although acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein and commonly measured autoantibodies are typically normal, abnormalities in immunoreactivity are believed to drive the inflammatory process. Patients with thromboangiitis obliterans have been shown to have increased cellular immunity to types I and III collagen compared with those who have atherosclerosis. In addition, high titers of antiendothelial cell antibodies have been detected in patients with this disorder.

Prothrombotic and hemorheologic factors may also play a role in the pathophysiology of thromboangiitis obliterans. The prothrombin gene mutation 20210 and the presence of anticardiolipin antibodies are associated with an increased risk factor for the development of the disease. Polymerase chain reaction analysis demonstrated DNA fragments from anaerobic bacteria in both arterial lesions and oral cavities of patients with thromboangiitis obliterans but not in arterial samples from healthy control subjects.
Thromboangiitis obliterans involves 3 phases: acute, subacute, and chronic (Figure 1). The acute phase is composed of an occlusive, highly cellular, inflammatory thrombus. Polymorphonuclear neutrophils, microabcesses, and multinucleated giant cells are often present. The chronic phase is characterized by organized thrombus and vascular fibrosis that may mimic atherosclerotic disease. However, thromboangiitis obliterans in any stage is distinguished from atherosclerosis and other vasculitides by the preservation of the internal elastic lamina.

Clinical Presentation
Patients with thromboangiitis obliterans typically present with ischemic symptoms caused by stenosis or occlusion of the distal small arteries and veins. Involvement of both the upper and lower extremities and the size and location of affected vessels help distinguish it from atherosclerosis. Although symptoms may begin in the peripheral portion of a single limb, thromboangiitis frequently progresses proximally and involves multiple extremities.

Arterial occlusive disease resulting from thromboangiitis obliterans often presents as intermittent claudication of the feet, legs, hands, or arms. Symptoms and signs of critical limb ischemia, including rest pain, ulcers, and digital gangrene, occur with more advanced disease. Raynaud’s phenomenon is present in >40% of patients with thromboangiitis obliterans and may be asymmetrical. Although most common in the extremities, thromboangiitis obliterans may also involve the cerebral, coronary, renal, mesenteric, and pulmonary arteries.

Superficial thrombophlebitis differentiates thromboangiitis obliterans from other vasculitides and atherosclerosis, although it may also be observed in Behçet’s disease. Superficial thrombophlebitis may predate the onset of ischemic symptoms caused by arterial occlusive disease and frequently parallels disease activity. Patients may describe a migratory pattern of tender nodules that follow a venous distribution.

The physical examination of a patient with suspected thromboangiitis obliterans includes a detailed vascular examination with palpation of peripheral pulses, auscultation for arterial bruits, and measurement of ankle:brachial indices. The extremities should be inspected for superficial venous nodules and cords, and the feet and hands should be examined for evidence of ischemia. Although nonspecific, a positive Allen test in a young smoker with digital ischemia is strongly suggestive of the disease. Neurological examination may document peripheral nerve involvement, with sensory findings in up to 70% of patients.

Diagnosis
Thromboangiitis obliterans is a clinical diagnosis that requires a compatible history, supportive physical findings, and diagnostic vascular abnormalities on imaging studies (Figure 2). Several criteria have been proposed for the diagnosis of thromboangiitis obliterans. Common
and to define the anatomy and extent of disease (Figure 3). Although advances in computed tomographic and magnetic resonance angiography show promise for imaging distal vessels, most patients require invasive contrast angiography to provide the spatial resolution necessary to detect small-artery pathology. Distal small- to medium-artery involvement, segmental occlusions, and “corkscrew”-shaped collaterals around areas of occlusion are typical angiographic findings in thromboangiitis obliterans. Proximal arteries should be normal without evidence of atherosclerosis. Biopsy is rarely indicated but is most likely to be diagnostic in a vein with superficial thrombophlebitis during the acute phase of the disease.

**Prognosis**

The prognosis for patients with thromboangiitis obliterans depends largely on the ability to discontinue tobacco use. In a retrospective series of 110 patients with thromboangiitis obliterans, 43% of patients underwent 108 amputation procedures. Among those who continued smoking, 19% required a major amputation. None of those who stopped smoking underwent amputation. A substantial proportion (85%) of patients with thromboangiitis obliterans who underwent major amputation lost their jobs.

**Management**

Discontinuation of tobacco use is the definitive therapy for thromboangiitis obliterans (the Table). Complete smoking cessation is essential because even a few cigarettes a day may result in disease progression. Patient education on the role of tobacco exposure in the initiation, maintenance, and progression of the thromboangiitis obliterans is paramount. Adjunctive measures to help patients discontinue tobacco use such as pharmacotherapy and smoking cessation groups should be offered. Nicotine replacement therapy should be avoided because it may contribute to disease activity. Although patients with thromboangiitis obliterans are thought to have a greater degree of tobacco dependence than those with coronary atherosclerosis, no significant difference in time to tobacco cessation after diagnosis has been demonstrated.

Surgical revascularization is usually not feasible in patients with thromboangiitis obliterans because of the distal and diffuse nature of the disease. However, bypass surgery may be considered in select patients with severe ischemia and suitable distal target vessels. Thromboangiitis obliterans patients undergoing bypass surgery often have suboptimal outcomes with primary patency rates of 41%, 32%, and 30% and secondary patency rates of 54%, 47%, and 39% at 1, 5, and 10 years. Graft patency rates are nearly 50% lower in patients with

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**Table. Clinical Pearls for Tobacco Cessation in Patients With Thromboangiitis Obliterans**

Educate patients on the role of tobacco in the initiation, maintenance, and progression of thromboangiitis obliterans

Counsel patients and members of their households about secondhand smoke exposure, which can perpetuate the disease process

Measure urinary nicotine and cotinine in patients who continue to have active disease despite claims of tobacco cessation

Offer adjunctive therapies, including pharmacotherapy and smoking cessation groups, to assist with discontinuation of tobacco use

Use bupropion and varenicline as the preferred agents to assist in smoking cessation because nicotine replacement therapy may contribute to disease activity

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clinical criteria include age <45 years; current or recent history of tobacco use; distal extremity ischemia confirmed by noninvasive testing; exclusion of thrombophilia, autoimmune disease, diabetes, and a proximal source of emboli; and consistent angiographic findings.1 Laboratory testing in patients with suspected thromboangiitis obliterans is used to exclude alternative diagnoses. Initial laboratory studies should include a complete blood count, metabolic panel, liver function tests, fasting blood glucose, inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein, cold agglutinins, and cryoglobulins. In addition, serological markers of autoimmune disease, including antinuclear antibody, anticientromere antibody, and anti-SCL-70 antibody, are detected in some patients with thromboangiitis obliterans but may also indicate an isolated thrombophilia. Lupus anticoagulant and anticardiolipin antibodies are detected in a vein with superficial thrombophlebitis during the acute phase of the disease.

*Figure 3. Invasive contrast angiography in a 28-year-old female smoker with thromboangiitis obliterans, severe secondary Raynaud’s phenomenon, and digital ischemia culminating in gangrene of her left index finger. Her aortic arch and proximal upper-extremity arteries are free of atherosclerosis (A). However, angiography of her left hand demonstrates numerous digital artery occlusions and an incomplete palmar arch (B).*
thromboangiitis obliterans who continue to smoke after surgery.10

Additional therapeutic options for the treatment of thromboangiitis obliterans have been limited to vasodilators, intermittent pneumatic compression, spinal cord stimulation, and peripheral periarterial sympathectomy. In a randomized controlled trial of 152 patients with the disease, patients treated with the prosta
donoid vasodilator iloprost had significant relief of rest pain, greater healing of ischemic ulcers, and a two-thirds reduction in the need for amputation.11 Other vasodilators such as α-blockers, calcium channel blockers, and sildenafil may be helpful but have not been studied in prospective clinical trials. Intermittent pneumatic compression of the foot and calves has been used to augment perfusion to the lower extremities in patients with severe claudication or critical limb ischemia who are not revascularization candidates because of distal arterial occlusive disease, including thromboangiitis obliterans.12 Epidural spinal cord stimulation has been shown to improve regional perfusion in patients with thromboangiitis obliterans.13 Peripheral periarterial sympathectomy is occasionally considered for patients with refractory pain and digital ischemia but remains controversial.

The limited options for patients with severe distal peripheral artery disease and critical limb ischemia have driven a growing interest in therapeutic angiogenesis.14–17 Although short-term results of therapeutic angiogenesis have been promising, long-term safety and efficacy require further investigation.18

Case Presentation

Venous ultrasonography documented superficial thrombophlebitis of the right lesser saphenous vein, which was the cause of the patient’s right leg pain. Magnetic resonance angiography demonstrated occlusion of the distal superficial femoral artery and distal pedal arteries. The left femoral-to-peroneal artery bypass graft was patent. Given the clinical diagnosis of thromboangiitis obliterans, the patient was educated on the importance of smoking cessation to limit the progression of the disease and to preserve the viability of his limbs. He was referred for smoking cessation counseling and agreed to consider adjunctive therapy with bupropion or varenicline. His immunosuppressive therapy was tapered and discontinued because it is not effective in thromboangiitis obliterans. In follow-up, the patient had successfully quit smoking and reported progressive improvement in his symptoms.

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Disclosures

None.

References