

# A challenging case of thromboangiitis obliterans

Contributions from several hospital services, including vascular surgery, acute pain management, and rheumatology, were needed to resolve the diagnostic and therapeutic complexities of an uncommon occlusive vascular condition in a young female smoker.

**ABSTRACT: Thromboangiitis obliterans, or Buerger disease, is a rare, idiopathic, occlusive vascular disease that is strongly associated with smoking and tobacco use. Among patients with peripheral vascular disease, reported prevalence ranges from 45% to 63% in India and 16% to 66% in Korea and Japan, to 0.5% to 5.6% in Western Europe and 0.75% in North America. Establishing the diagnosis and managing the disease in a timely way pose significant challenges because an extensive workup is required to rule out other causes of arterial occlusion, and no clear evidence-based management guidelines are available. The case of a young female smoker who was diagnosed with thromboangiitis obliterans after a thorough workup for distal arterial occlusions of the lower limbs highlights some of the diagnostic, logistic, and therapeutic challenges encountered with this uncommon disease.**

## Case data

A previously healthy 23-year-old female was being treated as an outpatient for seronegative asymmetric oligoarthritis. She had received trials of methotrexate, hydroxychloroquine, and sulfasalazine to suboptimal effect, and had experienced an initially positive response to prednisone. Her symptoms began worsening a few months later and she presented with the new complaint of a cold sensation in her extremities. A vascular ischemic process was suspected and urgent referral to vascular surgery was made. In the interim, she was diagnosed with Raynaud phenomenon at a visit to the emergency department. At her follow-up clinic visit, she was found to have worsening claudication, cold and mildly cyanotic feet, and a nongangrenous 1-cm dark purple skin lesion on the lateral sole of her foot. Because of concerns about progressive and worsening arterial ischemia, she was admitted to hospital to expedite the investigations needed for suspected vasculitis and consideration of other vasculopathies. Aside from asthma and intermittent diarrhea, her medical history was unremarkable. Notably, the patient was a heavy smoker and had increased her tobacco consumption leading up to presentation.

Following admission to hospital, the lesion on the patient's foot ex-

panded to become a 5-cm black lesion with necrotic appearance and was accompanied by evidence of digital ischemia (Figure 1). The patient later developed multiple lesions on the soles bilaterally, which were consistent with superficial phlebitis. Biopsy of the primary lesion revealed mild perivascular lymphocytic and inflammatory cell infiltrate with no evidence of a classic vasculitis or findings suggestive of any alternate diagnosis.

Based on the initial presentation and investigations, the working diagnosis was primary vasculitis with seronegative arthropathy. The differential diagnosis had originally included secondary vasculitis, atherosclerotic peripheral arterial disease, thrombosis due to a hypercoagulable state, and proximal source of emboli. Basic hematologic and metabolic parameters, including lipid levels and renal and liver function, were within the normal range. Aside from an ele-

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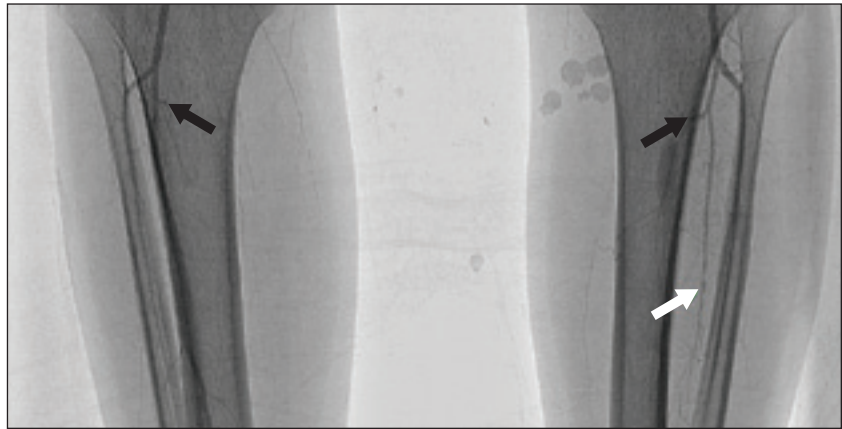
**Figure 1.** Cutaneous lesion on the lateral sole of a patient with thromboangiitis obliterans.

Evidence of digital ischemia can be seen in the distal part of the second and third toes.

vated rheumatoid factor of 46, results from her full rheumatologic workup were negative. Screening tests were also negative for hypercoagulable states, cryoglobulinemia, diabetes, and infectious diseases, although she did have a strongly positive purified protein derivative test result. A recent outpatient colonoscopy for a history of chronic diarrhea showed no evidence of inflammatory bowel disease. A transthoracic echocardiogram did not identify infectious endocarditis. CT angiography findings of the lower extremities were suggestive of a vasculitic process. A subsequent femoral arteriogram showed bilateral segmental occlusive disease of the distal lower limb vasculature with sparing of the proximal arteries (Figure 2 and Figure 3).

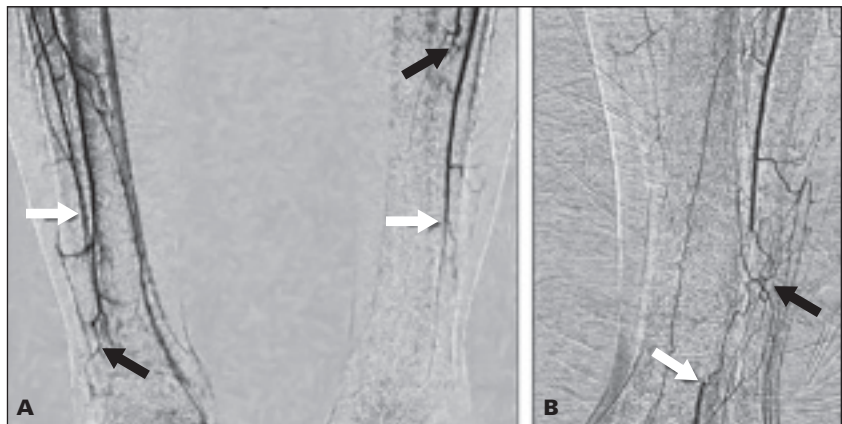
Following the thorough diagnostic workup and given the patient's young age, heavy smoking history, angiographic findings, and lab test results that were mostly in the normal range, a diagnosis of thromboangiitis obliterans (TAO), also known as Buerger disease, was felt to be likely. The final diagnosis was made 2 weeks after admission, following trials of several therapies.

At admission, the patient was taking 10 mg of amlodipine once daily



**Figure 2.** Distal lower limb vasculature of a patient with thromboangiitis obliterans as revealed on a femoral arteriogram.

The posterior tibial arteries are occluded bilaterally near the origin (black arrows). The left peroneal artery shows focal areas of stenosis and becomes occluded by mid-calf (white arrow).



**Figure 3.** Alternate views of the distal lower limb vasculature on the arteriogram of a patient with thromboangiitis obliterans.

**A:** The right peroneal artery is occluded a few centimetres above the ankle (black arrow, lower left), while the left peroneal artery tapers and becomes occluded by mid-calf (black arrow, upper right). Occlusion of the anterior tibial arteries can also be seen (white arrows). **B:** The left anterior tibial artery is better visualized at a later contrast filling phase. There is a long segmental occlusion in the distal calf and reconstitution of flow (white arrow) by collateral vessels (black arrow).

for Raynaud phenomenon. This was subsequently discontinued when no improvement was noticed. After the TAO diagnosis, the patient was able to successfully quit smoking. When conventional analgesics did not provide adequate pain control, the patient underwent a right lumbar sympathectomy. Concurrently, she received a 72-hour trial of intravenous epoprostenol, a synthetic prostacyclin analog.

Following that, heparin was administered but discontinued after 5 days when no benefit was perceived and a psoas hematoma developed at the sympathectomy site. The patient received other therapies thought to be of potential benefit, including 81 mg of acetylsalicylic acid (ASA) daily and 0.6-mg nitroglycerin patches applied to both feet daily; however, these offered little to no relief.

Over the course of the patient's 4-week hospital stay, the cutaneous lesions increased in size and number. She also developed digital ischemia in the second and third toes of her right foot. At the time of discharge, there was marked stabilization of disease progression and adequate pain control. When the patient was readmitted for pain management 1 month after discharge, her ischemic toes were found to have become necrotic and were affected by osteomyelitis. She received a course of intravenous antibiotics, and underwent a repeat lumbar sympathectomy that has controlled her pain to date.

## Discussion

Thromboangiitis obliterans, or Buerger disease, is a rare, idiopathic, occlusive vascular disease that is strongly associated with smoking and tobacco use.<sup>1-4</sup> The true prevalence is not known and estimates are highly variable. Among patients with peripheral vascular disease, reported prevalence ranges from 45% to 63% in India and 16% to 66% in Korea and Japan, to 0.5% to 5.6% in Western Europe and 0.75% in North America.<sup>3,4</sup> The reported North American incidence is 8 to 12.6 cases per 100 000 people.<sup>4</sup> To our knowledge, data are not currently available on the incidence and prevalence of TAO in Canada specifically. Though more common in males, the incidence of TAO is reported to be rising among females, likely due to increased rates of smoking.<sup>2,4</sup> According to one estimate, 8% to 20% of North American TAO patients are women.<sup>4</sup>

The diagnostic criteria for TAO vary slightly but the generally accepted criteria are described by Shionoya and others,<sup>5</sup> and are outlined in the accompanying **Table**. The patient described in this case report met all of the criteria and her arteriogram

findings were remarkably characteristic for TAO. The characteristic findings are described by Mills in a comprehensive review article: proximal vasculature sparing, segmental occlusion, frequent involvement of anterior and posterior tibial arteries, and development of collaterals.<sup>4</sup> The diagnostic process for TAO requires an extensive workup to exclude other diagnoses, and the time-consuming nature of the process can delay treatment and potentially affect outcomes.

There are no unanimously accepted treatment guidelines for TAO. The only recognized therapeutic mainstay is complete abstinence from tobacco products and smoking (including marijuana).<sup>1-4,6</sup> Continued smoking is associated with increased morbidity, as seen in a prospective cohort study of 89 patients followed for a mean of 91.6 months that found amputation rates to be 42% in patients who continued to smoke and only 5% in those who quit.<sup>7</sup>

Other treatment strategies are broadly divided into surgical and pharmacological therapies.<sup>6</sup> Lumbar sympathectomy for pain relief and promotion of vasodilation is the major surgical therapy for lower extremity TAO. In his review, Nakajima claims distinct clinical improvement in more than 60% of patients receiving this intervention in one study.<sup>8</sup> However, he acknowledges that the practice of sympathectomy has declined sharply and is rarely used today, likely because of the increasing popularity of noninvasive pharmacological approaches.<sup>8</sup> Our patient seemed to have benefited from sympathectomy, although it is difficult to distinguish precisely between the effects of the various other therapies tried given the overlap in timing. Other therapies described in the literature include arterial reconstruction and therapeutic angiogenesis with vascular endothe-

**Table. Diagnostic criteria for thromboangiitis obliterans.**

- Smoking or tobacco use
- Onset at less than 45 to 50 years of age
- Infrapopliteal, segmental arterial occlusions with sparing of the proximal vasculature
- Frequent arterial involvement in the distal upper extremities as evidenced by Raynaud phenomenon or digital ulceration
- Superficial phlebitis
- Exclusion of diabetes, arteriosclerosis, true arteritis, proximal source of emboli, and hypercoagulable states

lial growth factor gene transfer and tibial intramedullary Kirschner wire placement; while apparently promising, these interventions are still in the experimental phase.<sup>6</sup>

Pharmacological therapies are mostly geared toward maximizing and maintaining blood flow. The strongest evidence comes from a well-designed prospective randomized double-blind trial that compared the effects of a prostacyclin analog, intravenous iloprost, with low-dose oral ASA (100 mg daily) administered for 28 days.<sup>9</sup> The study showed iloprost to have clearly superior outcomes, with a positive response in 85% of the iloprost group compared with only 17% of the ASA group. Moreover, 18% of the ASA group eventually required amputation compared with only 6% of the iloprost group. A number of other strategies, including the use of cyclophosphamide, have been considered but without promising results.<sup>6</sup> Bosentan, an endothelin receptor antagonist, has appeared to be effective in improving blood flow detected on magnetic resonance imaging in one pilot study of 12 patients.<sup>10</sup> Anticoagulation agents may be used, but potential complications must be considered, especially if a sympathectomy is done; our patient developed a psoas hematoma at the surgical site while on heparin. Fur-

thermore, it is not clear whether anticoagulants confer any benefit as this topic is poorly studied.

We encountered many challenges in managing this case. Given the acuity and rapid progression of ischemia in an otherwise healthy young female, the lack of a curative therapy was traumatizing for the patient and difficult for the medical team. In addition to recommending smoking cessation and sympathectomy, the vascular surgery and rheumatology services agreed that iloprost should be administered. This posed a problem because iloprost is not available in Canada. We therefore opted for a trial of epoprostenol. Providing a patient with epoprostenol in British Columbia can also be a challenge, depending on facility resources and monitoring capabilities. Managing pain due to the critical limb ischemia was another challenge throughout the patient's hospital stay and after. The acute pain management service assisted the patient greatly by providing a multifaceted regimen. This included high-dose opiates with a period of patient-controlled analgesia, neuropathic pain medications that included gabapentin and amitriptyline, and, ultimately, a lumbar sympathectomy—the intervention that seemed to help the most.

Based on the prevalence rates quoted earlier, this is a disease that most generalist physicians will probably be exposed to during their careers. The expertise for diagnosis and management of this condition, however, is found in multiple specialties and subspecialties. Historically, vascular surgery has been the subspecialty with the most experience in managing TAO. In some countries, expertise resides within the field of vascular medicine, a subspecialty that does not exist in Canada currently. Due to similarities in the clinical presentations of thromboangiitis obliterans

and systemic vasculitis, TAO is also encountered in rheumatology and internal medicine, and management may require expertise from additional specialists for interventions such as sympathectomy and specialized pain management. While the differential diagnosis for TAO can include systemic vasculitis, as is the case with vasculitis-mimics such as moyamoya disease and Degos disease, this condition is not treated with immunosuppressive therapy since no clear benefit has been shown in experimental studies<sup>6</sup> and the risks of cytotoxicity and immunosuppression outweigh any theoretical benefit. The patient in this case later developed osteomyelitis following ischemia, and immunosuppressive therapy could have been detrimental if continued.

Given the complexity of diagnostic considerations and therapeutic approaches, a multidisciplinary approach is best for acute presentation as well as for outpatient follow-up, with early consultation between vascular surgery, acute pain management, and rheumatology services to provide balanced and multifaceted care.

### Summary

This case of a young female smoker diagnosed with thromboangiitis obliterans illustrates the diagnostic, logistic, and therapeutic challenges encountered with this uncommon disease. The condition of this patient was stabilized after a 4-week hospital stay, during which she quit smoking and received a variety of treatments, including a lumbar sympathectomy for pain relief and promotion of vasodilation.

Although limited management recommendations can be made from our experience with this one case, we can say it is important to recognize the changing epidemiology of the disease. In addition, more needs

to be learned about the pathology of a disease that has no highly effective medical treatments at present beyond smoking cessation and prostacyclin infusion. Finally, further research is needed to produce more evidence-based management guidelines for the therapies that do exist currently.

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### Competing interests

None declared.

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