Blue Toe Syndrome in Behçet’s Disease: A Case Report

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Patient: Male, 49-year-old
Final Diagnosis: Blue toe syndrome
Symptoms: Painful • bluish discoloration of the toes
Clinical Procedure: —
Specialty: Rheumatology • Surgery

Objective: Unusual clinical course
Background: Vascular Behçet’s disease (VBD) is a rare but potentially life-threatening subtype of Behçet’s disease that is characterized by multisystemic vasculitis. It primarily affects males with ancestry traced back to regions along the ancient Silk Road. Both arteries and veins, regardless of size, may exhibit complications, including aneurysmal degeneration or occlusion. While venous involvement is observed in two-thirds of VBD cases, arterial complications are notably the most severe and lethal. Arterial aneurysmal degeneration is more common than occlusive complications, with larger arteries being predominantly affected in VBD. Data regarding isolated small-vessel arterial occlusive disease in VBD are limited. Given the rarity of this presentation in this patient population, it becomes mandatory to thoroughly evaluate such patients to differentiate small-vessel vasculitis from other similar diseases, such as Raynaud’s phenomenon, which has a different etiology and management and generally has a more benign course. Here, we delineate the concept of isolated small-vessel vasculitis as a cause of blue toe syndrome in patients with VBD.

Case Report: This report describes a distinctive case of vascular Behçet’s disease in a 51-year-old man who initially exhibited unilateral blue toe syndrome, which swiftly progressed to dry gangrene of the toes. Despite reports of large-vessel involvement, there is a paucity of data on isolated small-vessel vasculitis-induced digital ischemia in VBD.

Conclusions: This atypical case underscores the necessity of clinical discernment in differentiating inflammatory microvascular occlusive disease from vasospastic Raynaud’s syndrome, both of which can complicate Behçet’s disease.

Keywords: Vascular Diseases • Peripheral Arterial Disease • Amputation • Chronic Limb-Threatening Ischemia • Digital ulcers

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Behçet’s disease (BD) is a rare, chronic multisystemic autoimmune disorder that affects various systems in the body, including the integumentary, mucosal, ocular, and vascular systems. First described in 1937 by Turkish dermatologist Hulusi Behçet, BD is characterized by recurrent oral and genital ulcers, epididymitis, uveitis, arthralgias, and various dermatological manifestations such as erythema nodosum and pyoderma gangrenosum [1]. The disease is most common in the Mediterranean, Middle Eastern, and Far Eastern regions, presenting diverse clinical symptoms that often pose diagnostic challenges [2,3]. While the exact etiology of BD is still unknown, it is believed to result from a combination of genetic and environmental factors. A meta-analysis by De Menthon et al [4] revealed a significant association between the HLA-B51/B5 allele and an increased risk of BD. Vascular Behçet’s disease (VBD), a severe form of BD, is mainly characterized by inflammation and damage to blood vessels, which can affect arteries and veins of different sizes, leading to development of aneurysms, thromboses, or obstructions within the vascular system, with arterial complications being less common than venous ones. This article introduces the case of a 51-year-old man residing in northern Jordan—a region with one of the highest global rates of BD [5]—who had a documented history of BD, assigned according to the International Criteria for BD (ICBD) after suffering from recurrent oral and scrotal ulcers, as well as residual scrotal scars. This patient experienced lower-limb ischemia due to vasculitis and occlusion in small- and medium-sized arteries. The literature on this topic is limited, with only a few case reports describing similar presentations. Our focus was on this rare presentation and how to distinguish it from other well-known diseases, especially Raynaud’s phenomenon (Table 1).

### Case Report

Our patient was a 51-year-old man with a history of Behçet’s disease diagnosed at the age of 49 by his rheumatologist after presenting with recurrent oral and scrotal ulcers, as well as residual scrotal scars. At follow-up, he presented with unilateral, extremely painful, bluish discoloration of the toes on his left foot, persisting for 3 weeks. He had no history of diabetes mellitus, hypertension, or ischemic heart disease, and no known family history of Behçet’s disease. He had never smoked and was not a second-hand smoker. He reported taking 1 mg of colchicine twice daily and 5 mg of prednisolone once daily. He had no prior episodes similar to this one. Initially, his rheumatologist managed him for Raynaud’s phenomenon, prescribing 20 mg of nifedipine twice daily, 400 mg of pentoxyfylline 3 times daily, and oral morphine as needed. However, his condition progressed to dry gangrene in the toes, necessitating referral to vascular services for further evaluation. Upon examination, vital signs were recorded as follows: equal normotensive readings in both upper extremities, a heart rate of 110 beats/min, a body temperature of 37.4°C, SpO2 at 97%, and a body mass index of 24.21 kg/m². Vascular evaluation indicated absent left anterior tibial and dorsalis pedis pulses, although a left posterior tibial pulse was palpable. The left foot showed well-defined dry gangrene affecting the toes (Figure 1), with no abnormalities detected in the right lower limb. Laboratory investigations revealed elevated inflammatory markers, with a CRP at 97 mg/L and an ESR at 45 mm/1 h. Although lipid profile, renal and liver function tests, and hepatic enzymes were normal, mild elevations were noted in alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) at 49 U/L and 103 U/L, respectively. White blood cell count was normal, but there was a moderate elevation in alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) at 49 U/L and 103 U/L, respectively.

#### Table 1. Blue toe syndrome differential diagnosis.

<table>
<thead>
<tr>
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<th>Blue toe syndrome</th>
<th>Raynaud’s phenomenon [33-36]</th>
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<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Auto-inflammatory/autoimmune</td>
<td>Stress/cold exposure</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Vasculitis</td>
<td>Vasospasm</td>
</tr>
<tr>
<td><strong>Structural changes</strong></td>
<td>Micro- or macro-vascular structural changes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Vessels affected</strong></td>
<td>Small arteries proximal to digital arteries</td>
<td>Digital arteries</td>
</tr>
<tr>
<td><strong>Symmetry</strong></td>
<td>More often Asymmetric</td>
<td>More often Symmetric</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>More severe</td>
<td>Less severe</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Usually progressive</td>
<td>Usually recurrent</td>
</tr>
<tr>
<td><strong>Inflammatory markers</strong></td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Signs and symptoms</strong></td>
<td>Pain and gangrene</td>
<td>Pain and triple-color change</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Anti-inflammatories, anti-coagulants, anti-platelets, vasodilators</td>
<td>Usually self-limiting; vasodilators, anti-platelets</td>
</tr>
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</table>
in platelet count at 680×10^3/mm³. Serology test results were unremarkable, including anti-phospholipid antibodies, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) PR3, and ANCA MPO. Glycated hemoglobin (HbA1c), thyroid function tests, thrombophilia profile, and electrocardiogram were all normal. A transthoracic echocardiogram revealed normal left ventricular function and anatomy, with no vegetations detected. Full-body CT angiography showed total occlusion of the distal left anterior tibial artery at the ankle level, as well as long-segment stenosis and areas of occlusion in the left dorsalis pedis artery. The later was distended with a thickened wall and showed tapering of contrast enhancement, suggesting vasculitis (Figure 2). No tandem proximal aneurysmal or occlusive arterial diseases in the systemic or pulmonary circulations were identified. A catheter-directed arteriogram of the left lower limb further elucidated the pathology in the distal foot, revealing total occlusion of the dorsalis pedis artery and weak plantar arch perfusion, despite patent posterior tibial and plantar arteries down to the mid-foot (Figure 3). Due to low perfusion of the plantar arch, the digital arteries could not be visualized with conventional angiography. This highlights the involvement of plantar microvasculature in the vasculitis process, in addition to the dorsalis pedis artery. Hospitalized for severe ischemic pain management and treatment of the active inflammatory process, the patient’s prednisolone dosage was increased to 30 mg daily. He was also given intravenous opioid analgesia, 300 mg of gabapentin twice daily, 30 mg of duloxetine once daily, and 4.5 g of intravenous piperacillin-tazobactam every 6 h. To prevent further thrombosis, therapeutic doses of enoxaparin (70 mg twice daily) and aspirin (100 mg daily) were initiated. Despite intensive medical therapy, the patient continued to experience intense forefoot pain, which only subsided after a forefoot amputation. Subsequently, he received a daily intravenous infusion of 60 micrograms of prostaglandin E1 (PGE1, Alprostadil) over 3 h to improve pain control by enhancing foot microcirculation. The rheumatology team concurred with this management approach and advised against adding azathioprine or other immunosuppressants due to the potential presence of an infectious process. After 9 days in the hospital, the patient showed significant improvement and was discharged with a detailed medication plan and scheduled follow-ups. Further clinical visits revealed a well-healed amputation site, resolution of ischemic symptoms, and a significant improvement in inflammatory markers, with CRP dropping to 14 mg/L. Tragically, the patient collapsed and died suddenly 2 months after discharge. According to his family, he had been experiencing left thigh pain in the days leading up to the incident. The next of kin, his wife, declined an autopsy due to religious beliefs, leaving the cause of death unknown. This unfortunate outcome underscores the grave prognosis associated with significant arterial involvement in vascular Behçet’s disease.

**Discussion**

Vascular Behçet’s disease (VBD) is a unique form of systemic vasculitis, impacting arteries and veins of all sizes [6]. Despite the incidence of Behçet’s disease (BD) being similar in both males and females, VBD is predominantly observed in men, exhibiting a male-to-female ratio of 9:1 [7]. Notably, vascular involvement usually manifests within the first 5 years following the appearance of other BD symptoms, affecting 15-38% of patients [8]. However, it is infrequently the initial clinical presentation, with oral and genital ulcerations being more common [9]. Approximately one-tenth of patients endure a vascular event preceding their BD diagnosis, with an additional 20% experiencing such events after diagnosis [10]. The 1990 International Study Group (ISG) criteria neglected to incorporate vascular involvement in their BD diagnostic criteria; this oversight was addressed in the 2014 International Criteria for Behçet’s Disease (ICBD) revision [7,11]. Venous diseases account for most vascular incidents associated with VBD, with venous lesions identified in 94% of VBD patients in one study [12]. While thrombosis can affect any segment of the venous system, arterial involvement, although less common, significantly contributes to morbidity and mortality [13,14]. Arterial involvement occurs in approximately 1.5-3% of patients globally, often presenting as multiple lesions accompanied by deep vein thrombosis [15-17]. This involvement primarily affects large arteries, particularly the aorta and pulmonary artery [15,18]. The course of mucous-cutaneous BD is generally indolent; however, arterial involvement can accelerate disease progression, with
Figure 2. Computed tomography angiogram of the distal left lower limb: Figure A shows patent enhancing left anterior tibial artery above the ankle (yellow arrow) with total occlusion distally at the ankle level (red arrow); Figure B shows calcified total occlusion segment of left dorsalis pedis artery (yellow arrow); Figure C shows re-opacified left dorsalis pedis artery distally with tapering of contrast enhancement; Figure D shows distended left dorsalis pedis artery distally with wall thickening. Features in Figures C and D are highly suggestive of vasculitis.
ruptured large arterial aneurysms being the primary cause of sudden death in BD patients [18]. Sasaki et al [19] highlighted the vulnerability of vascular reconstruction in VBD to anastomotic failure. Anastomoses constructed in angiographically and grossly healthy areas free of inflammation – with reinforced suture sites – may offer some advantages. Nonetheless, any vascular manipulation can induce inflammatory responses, adding to morbidity similar to the pathergy phenomenon observed in BD patients’ other organs [19]. Therefore, effective management of BD and its cardiovascular complications necessitates multidisciplinary collaboration among specialists, including physicians, cardiologists, cardiovascular surgeons, and endovascular interventionists. Digital ischemia in the lower extremities, attributed to small-vessel involvement, is an exceedingly rare presentation in VBD [20]. A comprehensive literature review yielded only a limited number of cases documenting isolated small-vessel-related limb ischemia in BD patients. Effective BD management requires a multidisciplinary approach wherein patients with vascular involvement primarily receive immunosuppressive agents supplemented by antithrombotic therapy following thromboembolic events [20]. Medical treatment optimization during the initial inflammatory phase is crucial before surgical interventions [3,17]. More severe cases may necessitate systemic anti-inflammatory therapy, including systemic corticosteroids, azathioprine, colchicine, thalidomide, or tumor necrosis factor-alpha inhibitors [20-23]. Notably, colchicine is employed for recurrent erythema nodosum, genital ulcers, and acute arthritis. Concurrently, glucocorticoids are used with immunosuppressive agents for treating BD-related uveitis, acute gastrointestinal, and pulmonary involvement [24,25]. Systemic PGE1 has also proven effective in treating BD-related ulcers unresponsive to other therapies [26]; it inhibits platelet aggregation and neutrophil activation, reduces blood viscosity, induces vasodilation, and significantly improves distal extremities’ microcirculation. These actions elevate transcutaneous oxygen pressures and expedite wound healing [26-28], in addition to alleviating vascular inflammation [29]. PGE1, along with immunosuppressants, has been used to treat vasculitis-related digital ischemia in patients with rheumatologic conditions like polyarteritis nodosa and rheumatoid arthritis [30-32]. The patient in this case report was successfully managed through both medical and surgical means, employing a combination of anti-platelets, steroids, colchicine, alprostadil (PGE1), and toe amputation. Although BD lacks a cure, symptom management allows patients to lead relatively normal lives. While many achieve remission or symptom resolution, approximately 5% of BD cases result in death, often due to vascular complications [22]. This particular case of BD primarily presented mucocutaneous lesions and vascular complications, with the patient uniquely exhibiting severe lower-limb digital ischemia due to occlusive vasculitis in relatively small-sized arteries, specifically the dorsalis pedis artery and plantar vascular arch. Unlike other limb ischemia cases necessitating major surgery due to large-vessel involvement, this patient showed no significant involvement of large vessels. Raynaud’s phenomenon (RP) is characterized by transient, recurrent, paroxysmal vasospasms of peripheral arteries, typically triggered by cold or emotional stress [33,34]. It usually affects the digits symmetrically and is often bilateral [35]. Onder et al documented a case of RP complicated by finger pad ulceration in a BD patient, successfully managed through a sympathetic nerve block [36]. In contrast, our patient experienced persistent unilateral non-recurrent inflammatory occlusion isolated to the left dorsalis pedis artery, resulting in reduced distal perfusion and gangrene in all left toes. This case emphasizes the importance of recognizing small-vessel involvement in BD and the necessity of distinguishing such atypical presentations from Raynaud’s vasospastic pathology. It advocates for further research to standardize the management of patients with limb ischemia related to BD.

**Conclusions**

The atypical presentation of VBD, evident in the form of small-vessel vasculitis-induced blue toe syndrome, should be distinctly identified and not mistaken for Raynaud’s phenomenon. An attentive approach to isolated microvascular involvement...
References:


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