A rare vascular manifestation in chronic myeloid leukemia: a case report and literature review of Bier's spot development during nilotinib treatment

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Abstract

Bier's spots are rare angiospastic macules often associated with physiologic vasoconstriction. This case report describes a 35-year-old man with chronic myeloid leukemia (CML) treated with nilotinib who developed Bier's spots, a previously unreported adverse effect of the drug. The patient presented with asymptomatic hypopigmented macules on the hands and legs that appeared during venous stasis and resolved with elevation. This case emphasizes the need to recognize potential vascular side effects of tyrosine kinase inhibitors (TKIs) and highlights Bier's spots as a benign but remarkable manifestation in patients undergoing nilotinib therapy.

Introduction

Angiospastic macules, also known as Bier's spots, are multiple, pale, irregularly shaped hypopigmented macules and patches that typically measure between 3 and 6 mm in diameter, with some reaching up to 10 mm. These spots have a reticulated pattern due to their contrast with the surrounding erythematous skin, which blanches with pressure, causing the macules to disappear transiently.[1] Bier's spots appear primarily on the extensor surfaces of the upper and lower extremities, often most prominently on the legs, but can occasionally have a generalized pattern.[2,3] Although predominantly affecting young adults, cases have been reported in individuals ranging in age from 15 to 75 years, with a male predominance of approximately 2:1. These spots are characterized by disappearance upon elevation of the limb or blanching of the surrounding skin. The lesions are more visible under conditions of emotional stress and less evident following physical activity, thereby highlighting their dynamic nature.[2]

The underlying etiology is attributed to hypoxia and venous stasis or venous hypertension, which provoke an exaggerated physiological vasoconstrictor response in small vessels.[4] They often appear on the forearm during external occlusion of venous blood flow and disappear when blood flow is restored. The spots increase in size and number with venous stasis when the extremities are lowered and disappear when venous return is restored by raising the limbs.[5] Diagnosis is typically clinical, based on the position-dependent disappearance of the macules, which can be further induced by applying a tourniquet to the affected limb. Histologically, these lesions have a normal skin appearance with no structural abnormalities.[2,3]

Nilotinib, a second-generation BCR-ABL tyrosine kinase inhibitor (TKI), has significantly improved the treatment of chronic myeloid leukemia (CML) and improved patient outcomes.[6] However, it has also been associated with adverse vascular events,

including angina pectoris, type 1 myocardial infarction, and peripheral arterial occlusive disease.[7,8] This report presents the first documented case of Bier's spots associated with nilotinib treatment, highlighting this drug's potential novel vascular side effect.

Case Report

A 35-year-old Saudi male smoker with a known history of CML presented to the outpatient clinic at King Fahad Specialist Hospital, Dammam, Saudi Arabia, with a chief complaint of multiple white patches on his hands and legs over the past six months. The lesions first appeared on his hands and then spread to his lower limbs. The macules were asymptomatic, transient, and triggered by straining or manual activity, resolving with elevation of the limbs or rest. The lesions remained unaffected by environmental factors, including humidity, temperature, and wind. The patient denied any associated symptoms, such as itching, burning, or pain. He had no history of trauma, infection, sexual activity, or other factors that could correlate with the appearance of the lesions. In addition, he had no history of dermatologic or vascular disease and had never experienced similar symptoms before.

The patient had been prescribed nilotinib since August 2016. Initially, he was on a dosage of 300 mg twice daily. Following a hematology evaluation in February 2022, his dosage was reduced to 400 mg once daily. At the time of his dermatology clinic visit in May 2024, he was still taking 400 mg once daily. Importantly, his dermatologic symptoms had started approximately six months earlier. At his last hematology clinic visit in October 2024, he was still on the 400 mg once daily regimen.

His medical history was unremarkable, and he reported no known allergies or medications. He smoked two cigarettes a day, which was considered unrelated to his main complaint since this habit had started years before.

On examination, the patient was afebrile and vitally stable with no constitutional symptoms such as fever, myalgia, arthralgia, night sweats, or weight loss. Physical examination revealed multiple well-circumscribed, round to irregular, hypopigmented macules ranging from 0.5 to 1.0 cm in diameter on the distal forearms, legs, dorsum of the hands, and feet (Figure 1). These macules were not associated with secondary lesions such as scaling, crusting, or ulceration but were surrounded by erythema. Provocative testing, by asking the patient to grasp his upper arm, induced further appearance of these macules on the distal forearm, which disappeared upon elevation of the limb (Figure 2). No other abnormalities, such as cyanosis, palpable lymph nodes, or organomegaly, were noted.

Based on the clinical findings and history, the diagnosis was angiospastic macules, commonly known as Bier's spots. Given the benign nature of this condition, the patient was reassured and advised to continue nilotinib as the therapeutic benefit outweighed the potential harm. No further diagnostic tests were performed, and the patient was scheduled for a follow-up visit in three months to monitor any changes in his condition.

Discussion

Bier's spots were first described by Bier in 1898 and have since been referred to by various terms, including exaggerated physiologic mottled macules of the skin, antispastic macules, and physiologic anemic macules.[2,9] These macules were initially thought to be a variant of nevus anemicus; however, unlike nevus anemicus, which is a congenital, permanent condition associated with adrenergic beta receptor deficiency in cutaneous blood vessels, Bier's macules are transient and result from physiologic vascular changes, distinguishing them as a separate entity.[10]

Bier's spots typically appear on the limbs but can also affect other regions, such as the face. For example, Yildiz *et al.*[11] described a case of white macules on the forehead that appeared with neck flexion and disappeared with neck extension. Similarly, Aytekin[12] reported unilateral white macules on the left side of the forehead that increased in visibility with the head down. Although usually localized, Bier's spots can also occur in a more generalized form, as described in an earlier case reported by Graham *et al.*,[13] who referred to it as exaggerated physiologic speckled mottling. The exact etiology of Bier's spots remains unclear, but evidence suggests that these macules result from vascular dysregulation. Using laser Doppler velocimetry, Gniadecki *et al.*[4] found that red spots were associated with increased blood flow and relative vasodilation,

Figure 1. Patient's hands with multiple small symmetrical white hypopigmented macules over slightly erythematous skin.

Figure 2. Patient's hands with multiple hypopigmented macules that fade and disappear when the patient's arms are raised.

whereas pale areas showed vasoconstriction. These findings were further supported by Dobrev *et al.*,[14] who used nailfold capillaroscopy to observe enlarged capillaries in affected areas. The diagnosis of Bier's spots is straightforward and relies primarily on clinical examination, which reveals numerous white macules with a blanching erythematous background that are position-dependent and disappear with limb elevation.[15] In the current case, the patient presented with asymptomatic hypopigmented macules on the extremities that were also position-dependent. Various triggers have been reported, including trauma, stress, and physical exertion. For example, Esme documented a case series in which one of his patients provoked the appearance of the macules through breath-holding.[16] In our case, the macules were provoked by clutching the hands, suggesting that physical strain may serve as a triggering factor. Differential diagnosis for Bier's spots includes conditions characterized by hypopigmented macules, such as pityriasis versicolor, vitiligo, achromic nevus, and post-inflammatory hypomelanosis.[2] Therefore, it is critical to differentiate Bier's spots from these conditions to avoid misdiagnosis and to recognize potential underlying systemic diseases that may manifest with similar cutaneous findings.[15,17] Bier's spots have been associated with several conditions, including lichen planus, alopecia areata, scleroderma, aortic hypoplasia varicosity, and Peutz-Jeghers syndrome, highlighting the need to evaluate for systemic involvement, especially in cases with widespread manifestations, which are often related to lymphedema, capillary malformation-arteriovenous malformation syndrome, tuberous sclerosis complex, pregnancy, and cryoglobulinemia, as these spots may be the first sign of these conditions.[2,9]

In our case, the appearance of Bier's spots coincided with the long-term use of nilotinib, a TKI commonly used in the treatment of CML. While TKIs, including nilotinib, have significantly changed CML treatment and improved patient outcomes, they have also been associated with vascular adverse events and vasculotoxicity, particularly in the peripheral and coronary arteries.[18] In our patient, nilotinib had been used for over seven years before the appearance of Bier's spots, which were induced by physical activities that likely triggered vasoconstriction and local hypoxia.

Vascular endothelial growth factor-A (VEGF-A) plays a critical role in human skin angiogenesis, acting as a specific mitogen for microvascular endothelial cells and promoting both angiogenesis and microvascular permeability. VEGF-A interacts with type III tyrosine kinase receptors primarily found on vascular endothelial cells. Under conditions of hypoxia, VEGF-A expression is upregulated in keratinocytes, fibroblasts, and endothelial cells.[3] Nilotinib, like imatinib, inhibits several protein kinases, including BCR-ABL, c-Kit, and PDGFR, thereby altering signaling pathways critical for vascular health.[19] Most documented cases of Bier's spots in the literature (*Supplementary Table 1*) have been attributed to idiopathic causes or associations with systemic diseases, with no previously established association with specific medications. However, our patient's long-term use of nilotinib suggests a possible association between TKI therapy and the development of Bier's spots, marking a novel association in the literature. This case highlights the need for clinicians to be vigilant for potential vasculotoxic side effects in patients undergoing TKI therapy and to consider Bier's spots as a possible, albeit rare, manifestation.[18] This observation is particularly significant as it highlights the potential for Bier's spots to occur as a side effect of long-term TKI use, prompting a broader differential diagnosis and recognition of associated vascular complications in patients treated with these agents. This case may be the first to link Bier's spots to nilotinib use and highlights the need for clinicians to consider drug-induced vascular manifestations in patients treated with TKIs.

Conclusions

This case highlights the importance for dermatologists to broaden their differential diagnosis when encountering Bier's spots and to consider potential associations with medications such as TKIs, especially in patients with chronic diseases such as CML. Recognition of this association may aid in the management and monitoring of similar patients to mitigate potential vascular side effects associated with TKI therapy.

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