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

Ahmed Alsaati,¹ Turki Hakami,² Sultan Bajawi,³ Gamil Mohammed,³ Nouf Bajawi,⁴ Nadya Al-Faraidy³

¹Department of Dermatology, Dammam Medical Complex, Ministry of Health, Dammam;

²Department of Dermatology, King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, Khobar; ³Department of Dermatology, King Fahad Specialist Hospital, Ministry of Health, Dammam; ⁴Jazan Health Cluster, Ministry of Health, Jazan, Saudi Arabia

Correspondence: Sultan Mohammed Bajawi, Department of Dermatology, King Fahad Specialist Hospital, Ministry of Health, 6408 Amer Bin Thabet - Al Muraikbat District, 32253, Saudi Arabia.

E-mail: medical.researcher12@gmail.com

Tel.: +966569780349

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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 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 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 so after physical activity, emphasizing 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 chronic phase 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, triggered by straining or manual activity, and resolved with elevation of the limbs or rest. The lesions were unaffected by environmental factors such as humidity, temperature, or 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 per day, which was considered unrelated to his primary complaint, as this habit had been initiated years before this complaint.

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 distinct entity.¹⁰

Bier's spots typically appear on the limbs but can also affect other regions, such as the face. For example, Yildiz and Saman¹¹ described a case of white macules on the forehead that appeared with neck flexion and disappeared with neck extension. Similarly, Aytekin¹² 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 and James,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 and Gniadecka⁴ found that red spots were associated with increased blood flow and relative vasodilation, whereas pale areas showed vasoconstriction. These findings were further supported by Dobrev and Nocheva,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. Vascular endothelial growth factor-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 (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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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.



Table 1. Case reports of Bier's spots in the literature.

First Author & Publication Date	Number of patients	Gender and Age	Manifestation and Factors	Body Involved	Co-Morbidities	Drug Medication and Histories	Diagnosis, Management, and Outcome
Bier (1898)	1	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Graham (1985)	1	20-year-old woman	Asymptomatic white macules over the limbs	Limbs	Unknown	Combined Oral Contraceptives	Diagnosis: Exaggerated Physiologic Speckled Mottling
Bessis (2002)	1	75-year-old woman	Multiple permanent white, ivory-like spots standing out from an erythrocyanotic background ranging from several millimeters to 10 cm in size with linear or circular roughly symmetrical pattern. The erythrocyanosis faded almost completely within minutes of lying down and quickly recurred within minutes of resuming standing position	Predominated on the trunk and proximal parts of the limbs, palms and soles. Involving mucous areas such as the tip of the tongue and middle part of the inner lower lip	Type II Mixed Cryoglobulinemia	Negative	Diagnosis: Diffuse Bier White Spots Management: Therapeutic attempt with oral nifedipine for one month was ineffective. Outcome: The outcome was marked by the occurrence of a stroke 6 months later with residual hemiplegia
Heller (2005)	1	34-year-old man	Generalized hypopigmented, 1-4 mm macules interspersed with blanching, erythematous macules. Lesions gave a reticulated, mottled appearance. Associated with dependency of the limbs and almost disappeared completely with limbs' elevation.	Trunk, upper extremities including the palms and lower extremities	History of tinea corporis treated without improvement.	Not mentioned	Diagnosis: Diffuse Bier Spots Management: Nifedipine 60 mg for 3 weeks then discontinued. Followed by loratadine 10 mg daily and Cimetidine 200 mg three times daily. Discontinued due to drowsiness. Outcome: Unknown
Peyrot (2006)	1	45-year-old woman	Small irregular asymptomatic permanent macules, standing on an erythrocyanotic background over the abdomen and lower limbs. Appeared with scleroderma renal crisis and disappeared with treatment and resolution of the crisis.	Abdomen and lower limbs	Systemic scleroderma with sclerodactyly, Raynaud's phenomenon, polyarthralgia, esophageal dysfunction, interstitial pneumopathy, malignant hypertension and scleroderma renal crisis	Not mentioned	Diagnosis: Uncommon Bier's spots associated with scleroderma renal crisis. Management: Treated by hemodialysis for 18 months and captopril plus prednisone at a dose of 1 mg/kg/day over 2 weeks and progressively reduced to a dose of 5 mg once daily after 14 months of treatment. Outcome: Bier's spots disappeared at 3-month follow-up.
Khera (2008)	1	27-year-old female	Multiple hypopigmented macules on the extensor surfaces of her upper and lower extremities. Upon raising her arms for several seconds or warming her skin, the lesions would dissipate. The lesions ranged in diameter from 1 mm to 10 cm and were arranged in a symmetric pattern	Extensors of Upper and Lower Extremities	Not Mentioned	Not Mentioned	Diagnosis: Physiologic Anemic Macules Management: No treatment and reassurance. Outcome: Not mentioned.
Tunca (2011)	2	Case 1: 11-year-old boy Case 2: 12-year-old girl	Case 1: Several irregularly shaped, white macules with diameter ranging from 2 to 5 mm on the dorsum of both hands and wrists. Positive dependent position. Positive blanching of the surrounding skin. Case 2: Numerous irregularly shaped, pale macules ranging in size from 2 to 7 mm and scattered on the dorsal aspect of her left forearm and hand on mildly erythrocyanotic skin background. Positive dependent position. Positive blanching of the surrounding skin.	Case 1: Dorsum of hands and wrists. Case 2: Dorsal aspect of left forearm and hand.	Unremarkable for both cases.	Not mentioned	Diagnosis: Bier Spots. Management: Not mentioned. Outcome: Not mentioned.
Mahajan (2015)	1	28-year-old male	Innumerable asymptomatic hypopigmented macular lesions with irregular borders and background blanching erythema in a mottled pattern over his forearms and hands with dependent position and disappeared on limb elevation	Forearms and Hands	Unremarkable	Negative	Diagnosis: Bier Spots Management: Not Mentioned Outcome: Not Mentioned

Yorulmaz (2015)	1	32-year-old male	Several scattered whitish macules, several millimeters in size, intermingling with erythrocyanosis of the affected parts with vascular mottling. Positive dependent position. Lesions became indistinguishable via diascopy. Lesions disappeared upon elevating his upper extremities above his head.	Distal parts of his upper and lower limbs. Both flexors and extensors were affected. More pronounced on upper extremities.	Unremarkable	Negative	Diagnosis: Spontaneous Bier Spots. Management: Not mentioned. Outcome: Follow-up was given but its details were not mentioned.
Yildiz (2016)	1	33-year-old man	Hypopigmented macular lesions with irregular border against a background of erythema over the face in the dependent position with raising of head.	Face (Forehead)	Smoker, Epilepsy, Insomnia, alopecia areata and deep venous thrombosis	Carbamazepine (Stopped at the age of 18)	Diagnosis: Bier Spot Management: No treatment was given. Outcome: Not mentioned.
Dobrev (2018)	2	Case 1: 34-year-old male Case 2: 20-year-old female	Case 1: White anemic macules with irregular shape that become larger and more visible at erythrocyanotic background when limb was suspended. Disappeared with elevation of extremities and cuff removal. Case 2: white anemic macules with irregular shape	Case 1: Upper Limbs Case 2: Volar aspects of her hands	Case 1: Unremarkable Case 2: Raynaud's Phenomenon	Case 1: Negative Case 2: Not Mentioned	Diagnosis: Bier Spots Management: No treatment was given for both cases. Outcome: Not mentioned for both cases.
Palamino (2020)	1	28-year-old female	Asymptomatic hypopigmented macules of 5 to 10 mm in diameter irregular pale, scattered on the forearms in a sloping position of the limbs, without any sign of atrophy and quickly disappearing when the arms were raised	Forearms	Unremarkable	Not Mentioned	Diagnosis: Bier's Spots Management: No treatment was given. Outcome: Not mentioned
Aytekin (2021)	1	40-year-old man	Multiple hypopigmented irregularly shaped patches distributed over the left side of the forehead and cheek. More visible with head-down position	Unilateral left side of the forehead and cheek	Negative	Negative	Diagnosis: Bier Spots Management: No treatment was given. Outcome: Not mentioned
Esme (2023)	3	Case 1: 45-year-old male Case 2: 48-year-old male Case 3: 32-year-old female	Case 1: pale whitish macules on the forehead after trauma, emotional stress and induced by bending down Case 2: Multiple whitish macules over the forehead and trunk, provoked by holding his breath about a half minute and bending down Case 3: Whitish macules over the forehead after vaginal delivery	Case 1: Face (Forehead) Case 2: Face and Trunk Case 3: Forehead	Case 1: Headache + Precipitated trauma (unspecified type) Case 2: Tension-type Headache Case 3: Tension-type Headache	Negative	Diagnosis: Bier Spots Management: 150 Speywood units (reconstituted with 2.5 ml normal saline) of botulinum toxin (AbobotulinumtoxinA, Dysport, Ipsen, 500 units) were injected to both Case 1 and 2. Case 3's management was not clear. Outcome: No response in Bier spots six weeks after botulinum toxin injection for both Case 1 and 2. Case 3's outcome was not mentioned.
Alsaati (2024) (Present Case)	1	35-year-old male	Multiple transient well-circumscribed rounded to irregularly shaped hypopigmented macules ranging in size from 0.5 to 1.0 cm in diameter. Positive position dependent.	Upper and lower distal extremities	Chronic Myeloid Leukemia - Chronic Phase	Imatinib in 2009. Dasatinib in 2010. Nilotinib since 2016 until present date.	Diagnosis: Bier's Spots Management: None. Outcome: Reassurance, and follow-up was given.