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CASE REPORT

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Bier anemic spots, cyanosis, and urticaria-like eruption (BASCULE) syndrome: Report of two new cases and literature review

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Abstract

We herein report two new adolescent cases of Bier anemic spots, cyanosis, and urticaria-like eruption (BASCULE) syndrome. This rare, recently described condition may be associated with postural orthostatic tachycardia syndrome (POTS) and other forms of orthostatic intolerance. This report provides details on two cases and a literature review.

KEYWORDS

BASCULE syndrome, bier anemic spots, cyanosis, orthostatic intolerance, postural orthostatic tachycardia syndrome, urticaria

1 | INTRODUCTION

Bier anemic spots, cyanosis, and urticaria-like eruption (BASCULE) syndrome was first described in 2016 by Bessis et al,[1] who reported four cases, two in infants and two in adolescents. We herein present two new cases of adolescents with BASCULE syndrome and review the literature.

2 | CASE 1

A 13-year-old overweight boy presented with a 2-week history of pain and pruritus associated with erythrocyanosis and red papules surrounded by an anemic halo on his lower limbs (Figure 1A,B) His symptoms occurred only while standing or in the pool and disappeared when lying down. No history of recent infection, fever, or arthralgia was found. His medical history was significant for Raynaud's phenomenon present for 1 year.

Laboratory tests, including a complete blood count, antinuclear antibody (ANA), rheumatoid factor (RF), thyroid studies, and urinalysis, were unremarkable. A 3.5-mm punch biopsy of an urticaria-like lesion revealed a nonspecific inflammatory lymphohistiocytic infiltrate surrounding the vessels of the upper dermis (Figure 2). Immunofluorescence antibody staining was negative.

The clinical and histopathologic findings were consistent with a diagnosis of BASCULE syndrome. Desloratadine 5 mg twice daily for 6 weeks proved ineffective. The patient was referred to pediatric cardiology for an active standing test in order to exclude postural orthostatic tachycardia syndrome (POTS) and other forms of orthostatic intolerance. Heart rate, blood pressure (BP), electrocardiogram (ECG), and echocardiogram were normal. Given the negative workup but patient's overweight status (weight: 76 kg, body mass index [BMI]: 28), physical exercise and dietary modifications alone were recommended without significant improvement.

3 | CASE 2

A 13-year-old girl presented with a 3-year history of ankle pain associated with pruritus, Bier spots (BS), and cyanosis of the legs when walking. Urticaria-like lesions after showering were also reported. Her symptoms resolved when lying down. A Doppler ultrasound, complete blood count, thyroid studies, and ANA were negative. Cardiac evaluation, including an ECG, echocardiogram,

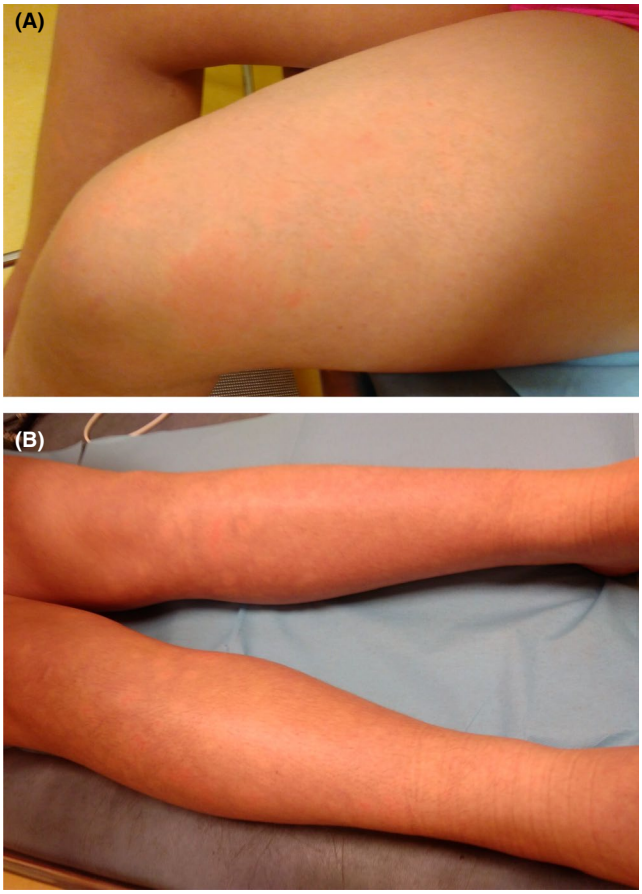

FIGURE 1 A-B, Erythrocyanosis associated with multiple red papules surrounded by an anemic halo

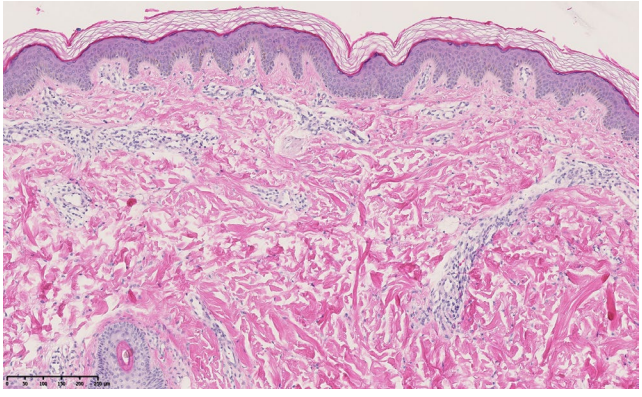

FIGURE 2 Histological findings showing a nonspecific inflammatory reaction around the upper dermis vessels

stress ECG, and active standing test, was normal, except for a slightly prolonged QT interval. Based on these findings, the diagnosis of BASCULE syndrome was made. The urticaria-like lesions did not respond to desloratadine 5 mg once daily for 1 month. Additional preventive measures were recommended, such as physical exercise and elevating the legs when possible without significant improvement.

4 | DISCUSSION

The clinical manifestations of BASCULE syndrome characteristically affect the lower limbs and occur 1-2 minutes after standing. Erythrocyanosis appears first, followed by anemic macules that then within minutes develop into pruritic orange-red papules extending from their center. All symptoms disappear spontaneously when lying down.[1] While BASCULE syndrome most commonly affects the legs, Jimenez-Gallo et al[2] recently described a case affecting the trunk and upper extremities.

To date, nine cases of BASCULE syndrome have been reported in the literature: two in newborns, in which the clinical manifestations were noted with dependency, and the remaining seven in adolescents (Table 1). Skin biopsies were obtained in five previously reported cases and in one of our cases (Case 1). These histological findings were generally non-specific, with only a few dilated capillaries in the upper dermis without any specific infiltrate noted in the majority of cases. An eosinophilic infiltrate was reported in two cases.[1-4] The findings thus resemble the non-specific findings of common urticaria: a sparse perivascular and interstitial mixed inflammatory infiltrate with edema in the upper dermis.[5] Evaluation to exclude coagulation disorders, thyroid or autoimmune disorders, neuropathic pain or venous insufficiency, including complete blood counts, coagulation studies, thyroid studies, ANA, RF, Doppler ultrasound, and electromyography, was normal in all cases. However, chronic orthostatic intolerance was diagnosed in three patients.

It has been suggested that the skin findings of BASCULE represent a benign vasomotor disorder. BS are due to a physiological venous stasis that likely induces an exaggerated vasoconstrictive response of arterioles to tissue hypoxia, as well as a lack of veno-arteriolar reflex in dermal ascending arterioles. The urticaria-like papules that arise from Bier spots in BASCULE may also result from a paradoxical reaction to hypoxia.[1] While Bier spots are primarily a physiological phenomenon, they have occasionally been associated with other conditions. For example, they can occur transiently during pregnancy and have been reported during renal crisis associated with scleroderma.[6]

While not observed in our cases, it is noteworthy that three published reports of BASCULE syndrome have occurred in association with different forms of chronic orthostatic intolerance; POTS, orthostatic hypotension, and syncopal episodes, respectively.[3,4,7] Six of the nine previously reported cases plus our two new cases were tested for POTS with only one positive outcome. POTS is a disorder of the autonomic nervous system that results in chronic orthostatic intolerance associated with tachycardia. The diagnosis first requires an active standing test or tilt-table test. A positive result consists of a heart rate increase by ≥30 beats per minute (bpm) within 10 minutes of standing in adults and ≥40 bpm in children and adolescents. Patients typically maintain or increase their BP when in an upright position. Associated symptoms include both cardiac (tachycardia, lightheadedness, chest discomfort, and dyspnea) and noncardiac (headache, leg pain, fatigue, anxiety, and exercise

TABLE 1 Reported cases of BASCULE syndrome

	Age/ Sex	Position	Symptoms	Laboratory test results, antibody tests, Doppler US	Histology	Cardiac symptoms	POTS/Orthostatic intolerance
Bessis et al[1,5]	14 y/F	Standing immobile	Typical	Normal	Eosinophilic infiltrate	None	POTS
	16 y/F	Standing immobile	Typical	NT	NT	None	Normal
	15 y/F	Standing immobile	Typical ankle edema	Normal	NT	None	NT
	19 y/M	Standing immobile	Typical	Normal	NT	None	NT
	4 m/M	Manual compression	Upper and lower limbs	NT	NT	None	NT
	4 m/M	Manual compression	Upper and lower limbs	NT	NT	None	Normal
Danescu et al[4]	11 y/F	Standing immobile	Upper and lower limbs Paresthesia	Normal	No infiltrate on the biopsy	Tiredness Sweating Light-headedness	Initial orthostatic hypotension
Martin. et al[2]	13 y/F	Standing immobile	Typical	Normal	No infiltrate on the biopsy	Three exercise-related syncopal episodes	Syncopal episodes
Jiménez-Gallo et al[2]	8 y/M	Standing immobile	Trunk upper limbs	Normal	Eosinophilic infiltrate	None	Normal
Current report	13 y/M	Standing immobile + In the pool	Typical tenderness	Normal	No infiltrate	Tenderness Pain on contact Exercise intolerance	Normal
	13 y/F	Standing immobile + In the shower	Typical ankle pain and edema	Normal	NT	Tenderness Pain on contact Exercise intolerance	Normal

Note: Typical: When symptoms of BASCULE syndrome occur 1-2 min after standing in the lower limbs and disappear spontaneously when lying down

Abbreviation: NT, not tested.

intolerance) manifestations, which classically worsen when standing and improve when lying down.[8-10] Approximately 50% of patients also develop lower extremity acrocyanosis when standing, as occurs in BASCULE.[8] A diagnosis of POTS is confirmed when symptoms persist for ≥6 months. Notably, the autonomic nervous system may change around the time of puberty or following an acute illness or other physical stressor. First-line therapy consists of behavioral and dietary modification, including exercise, increased water and salt intake, and compression stockings. Pharmacological treatments, including fludrocortisone, propranolol, desmopressin, midodrine, pyridostigmine, clonidine, or ivabradine may be administered as second-line therapy.[8-10] In our two cases and in published cases, antihistamine treatment was ineffective.[1-4] The prognosis of BASCULE syndrome is otherwise favorable, with skin lesions typically resolving after months to years.

Danescu et al reported a case of BASCULE syndrome associated with chronic orthostatic intolerance that presented as initial orthostatic hypotension, the most common form of orthostatic intolerance in young people.[4,10] Initial orthostatic hypotension is defined as a 40 mm Hg decrease in systolic BP and/or >20 mm Hg decrease in diastolic BP within 15 seconds of standing. The initial BP drop results from a mismatch between increased cardiac output and decreased systemic vascular resistance due to a failure of the autonomic nervous system. The BP rebound, in contrast, is due to sympathetic vasoconstriction in the peripheral vasculature.[4,8,10] BASCULE syndrome patients may also suffer from presyncopal or syncopal episodes which is the third form of orthostatic intolerance, without evidence of orthostatic tachycardia or orthostatic hypotension, such as described in Martín et al.[3,10]

Our two patients had non-cardiac symptoms, including leg pain only when standing and pain during exercise, but tested negatively for POTS and chronic orthostatic intolerance. However, Bessis et al described a patient with BASCULE and no associated symptoms that tested positive for chronic orthostatic intolerance, emphasizing the importance of evaluation even in otherwise asymptomatic patients.[3]

BASCULE syndrome is a benign vasomotor dermatosis characterized by typical clinical features including erythrocyanosis, generally of the lower extremities, with associated Bier spots that evolve quickly into pruritic urticarial-like papules. Symptoms classically occur with standing and resolve with lying down. The diagnosis is clinical, as histopathology is non-specific. However, patients suspected of having BASCULE syndrome, even if otherwise asymptomatic, should undergo evaluation for chronic orthostatic intolerance. We hypothesize that the association of these conditions is likely not random, but may reflect a common underlying pathology, a benign vasomotor disease.

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