Sickle cell crisis presenting as livedo racemosa

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Abstract

Sickle cell disease is a monogenic hemoglobinopathy that results in the abnormal production of hemoglobin S, which yields the characteristic sickle-shaped red blood cells. Sickle cell vaso-occlusive crisis is a painful complication of sickle cell disease caused by red blood cell entrapment within the microcirculation. The resulting tissue ischemia triggers a secondary inflammatory process involved in the pathogenesis of varying inflammatory skin conditions. Chronic leg ulcers are the most common skin presentation in sickle cell disease. A 58-year-old woman with sickle cell disease presented with systemic edematous plaques with the most notable involvement of her bilateral legs, which exhibited reticulated purpuric patches with central pallor. We report a case highlighting an unusual presentation of livedo racemosa as the presenting sign in a patient with sickle cell disease in vaso-occlusive crisis.

Keywords: crisis, livedo racemosa, livedo reticularis, sickle cell, vaso-occlusive

Introduction

Sickle cell anemia is an inherited autosomal recessive hemoglobinopathy characterized by the production of hemoglobin S due to a point mutation that changes glutamic acid to valine at position 6 within the hemoglobin beta gene [1]. Sickle cell disease occurs when two mutated alleles are inherited, causing increased production of abnormal red blood cells (RBC). Normal adult hemoglobin normally binds to four oxygen molecules and serves as a vehicle to distribute oxygen systemically. In individuals with sickle cell disease, abnormal hemoglobin S polymerizes under low oxygen environments forming the characteristic rigid sickle-cell shape. These sickled RBCs aggregate and become entrapped within the microcirculation, causing tissue ischemia and pain [1]. Complications of this disease's pathophysiology can manifest as hemolytic anemia, vaso-occlusion, and vasculopathy [2]. We report an unusual case of livedo racemosa as an associated sign of sickle cell crisis.

Case Synopsis

A 58-year-old woman with a history of sickle cell disease status post splenectomy, presented for evaluation of pruritic, burning eruptions that had been present for one week. She had visited the emergency department three times prior to visiting the dermatology clinic. She was treated for urticaria initially with oral corticosteroids and diphenhydramine and later with cetirizine and hydrocodone/acetaminophen. These treatments provided minimal relief and the patient reported that her lesions persisted. She noted associated joint pain and edema in her extremities. The patient reported having symptomatic lesions all over her body, but they were most prominent on her lower extremities. She had tried numerous commercially available topical treatments without improvement. She denied any medication changes and personal or family history of autoimmune conditions. She was

tested in the emergency department and was negative for COVID-19.

On examination, edematous plaques with peripheral pallor were scattered diffusely on the face, anterior neck, upper extremities, back, and buttocks. The most notable involvement was on the bilateral lower legs, which exhibited purpuric patches with central pallor in a reticular configuration (**Figure 1A**). There was also pitting edema of the bilateral dorsal hands and forearms and bilateral dorsal feet and lower legs.

The clinical findings were highly concerning for sickle cell vaso-occlusive crisis. A 4mm punch biopsy was obtained from the central pale area surrounded by a plexus network along the medial aspect of her right knee (**Figure 1B**). The patient was admitted from the clinic for further workup and treatment. The differential diagnosis also included antiphospholipid antibody syndrome and lupus erythematosus. Laboratory evaluation revealed negative ANA antibodies, antiphospholipid antibodies, and unremarkable rheumatoid factor levels. The biopsy revealed perivascular and interstitial chronic inflammatory infiltrate with RBC extravasation and prevalent dysmorphic, elongated RBCs (**Figure 2**). No vasculitis or thrombosed vessels were identified. The eruptions resolved after treatment for sickle cell vaso-occlusive crisis with intravenous fluids and pain management.

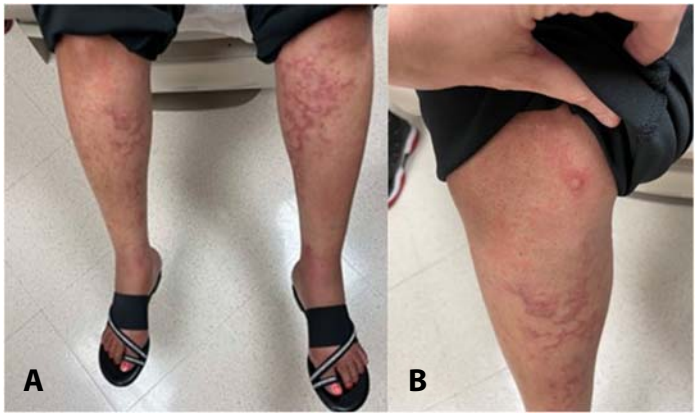

Figure 1. ***A)*** *Purpuric reticular patches with central pallor on the bilateral legs.* ***B)*** *Punch biopsy site along the medial aspect of right knee.*

Case Discussion

Sickle cell disease is one of the most morbid monogenic conditions worldwide [1]. Hemoglobin S forms from an amino acid switch from glutamic acid to valine, which alters the polarity of hemoglobin. In deoxygenated hemoglobin S, the abnormal amino acid substitution interacts with a hydrophobic pocket within other hemoglobin S molecules and produces insoluble filaments. These filaments, alongside electrolyte dysregulation, yield dense, dehydrated sickle-shaped RBCs that aggregate and occlude small vessels [3]. Additionally, damage to the endothelium upregulates the production of integrins, adhesion receptors that play a significant role in extracellular matrix communication, platelet aggregation, RBC adhesion to the endothelium, and cell-to-cell interactions [4,5]. As a result, the intrinsic predisposition of vaso-occlusion by sickled RBCs is exacerbated by other pro-inflammatory processes within the extracellular environment, leading to multi-organ consequences.

Sickle cell vaso-occlusive crisis is an acute painful phenomenon that occurs when the systemic vasculature is blocked. Like other chronic inflammatory conditions characterized by vasculopathy and hemolysis, sickle cell disease involves complement activation, triggering further inflammatory cascades. Activation of complement

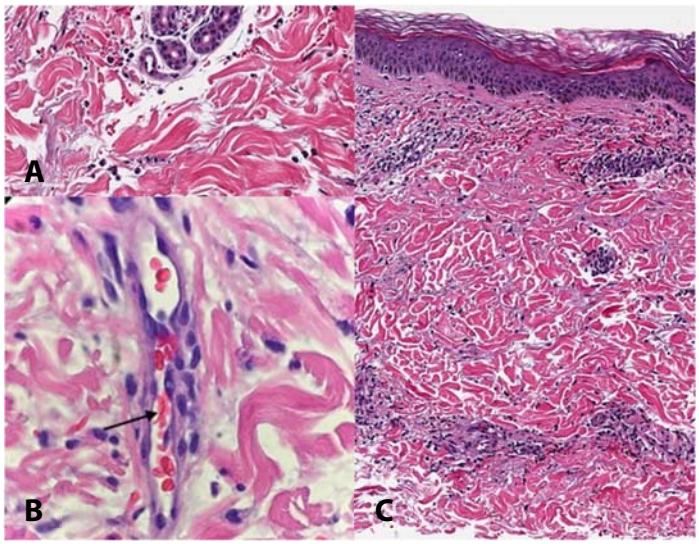

Figure 2. *H&E histopathology.* ***A)*** *Lesion biopsy demonstrating chronic interstitial inflammatory infiltrate that extends from the superficial to deep dermis, 20×.* ***B)*** *Lesion biopsy demonstrating red blood cell extravasation with red blood cells exhibiting dysmorphic and elongated features, 40×.* ***C)*** *Lesion biopsy depicting sickled red blood cells within the microvasculature as indicated by the black arrow, 100×.*

results in C3 split fragments that bind to the RBC surface, further contributing to the adhesion of dysmorphic RBCs to the inflammatory activated vascular endothelium and may result in RBC sequestration. Compared to healthy RBCs, the abnormal flow dynamics demonstrated by sickled RBCs reduce transit time within the microcirculation, thus possibly leading to microvascular injury and ischemia [6,7]. The infarcted tissue caused by in-situ sickling triggers a secondary inflammatory response and releases inflammatory mediators, including interleukin-1 (IL1), bradykinin, histamine, substance-P, and calcitonin gene-related peptide [8]. These inflammatory markers, specifically IL1, trigger local and systemic inflammatory responses such as fever, pain sensitivity, vasodilation, and leukocyte locomotion, which may play a role in the pathogenesis of inflammatory skin conditions [9]. Acute treatment of vaso-occlusive crisis involves symptomatic pain management, including non-opioid and opioid analgesics and intravenous hydration as given to our patient [10]. Hydroxyurea, which upregulates the production of fetal hemoglobin, is used to prevent future crises due to its relatively low adverse effect and high benefit profile [11].

Chronic leg ulcers are the most frequent cutaneous finding in sickle cell disease [12]. These lesions are marked by round, punched-out ulcers with raised margins and necrotic centers commonly located on the anterior tibia, foot dorsum, and ankle, with the medial malleolus more affected than the lateral malleolus [3].

Although purpuric patches associated with sickle cell disease have been rarely reported in the literature, to our knowledge, our case is the first reported case of livedo racemosa without ulceration as a cutaneous presentation in a patient with sickle cell disease in vaso-occlusive crisis [12]. Livedo racemosa is a cutaneous pathologic finding characterized by red-to-blue irregular, discontinuous, and branched reticular patches secondary to vascular occlusion. The lesions may present similarly to livedo reticularis but differ by location (livedo racemosa is typically more generalized and widespread and found on the limbs, trunk, and buttocks), morphology, and histopathology [13,14]. The distinction between the two livedo presentations is a relatively newer concept not mentioned in older literature. Livedo racemosa is associated with inflammatory and vaso-occlusive states such as Sneddon's syndrome, primary antiphospholipid syndrome, systemic lupus erythematosus, pancreatitis, and other vasculitis and embolization syndromes [15,16]. Treatment is often focused on addressing the underlying pathophysiology.

Livedo reticularis is a physiologic sign characterized by transient or persistent, red-to-purple, symmetric, net-like cyanotic patterns that can occur in various physiologic and pathologic states [13]. Physiologic livedo reticularis or cutis marmorata is a benign arteriolar vasospastic response to cold temperatures in which the superficial blood vessels contract and dilate simultaneously. With warming, the lesions should resolve. Pathologic livedo reticularis can be divided into congenital or acquired. Congenital livedo reticularis, also known as cutis marmorata telangiectatica congenita (CMTC), is a congenital condition that presents at or shortly after birth and typically affects the lower extremities. Although the lesions usually resolve with age, this condition is associated with other comorbidities, so a thorough evaluation is warranted in children with CMTC [17]. Acquired livedo reticularis can be idiopathic or secondary to systemic disease that can cause various vascular pathologic processes [13,18]. The clinical appearance of livedo reticularis results from the cutaneous arrangement of the microvasculature in which the ascending arterioles rise perpendicularly to the skin surface and form 1-3cm cones of arteriole predominance. The arterioles terminate superficially into a capillary bed, with the arteriole located centrally [18,19]. These capillary beds then drain into a subpapillary venous plexus at the periphery of the arteriolar conical bases. This is clinically significant because any reduction in blood flow to and from these capillary spaces can result in vascular congestion [17,18]. Histopathologic features of livedo reticularis include vessel wall thickening, arteriole obliteration, RBC aggregation, thrombi, and inflammation [19].

Due to the multiple etiologies that can result in livedo racemosa, various histopathologies have been observed. Pincelli et al. reviewed 33 patient cases and noted different pathologic findings, including organized thrombosis, intimal and subintimal wall thickening, lymphoplasmacytic vasculitis with thrombosis, neutrophilic vasculitis, granulomatous vasculitis, or no histological abnormalities [20]. Our patient did not exhibit all the classic features of livedo reticularis or racemosa as no thrombosis or vasculitis was evident. However, Jones et al. reported pathologic findings of sickle cell disease in vaso-occlusive crisis presenting as purpura consistent with ours, including the presence of RBC extravasation, dysmorphic, elongated RBCs, and perivascular inflammation. They also did not observe any thrombi or vasculitis [12]. Thus, in addition to our patient's symptoms and history, the observed histopathologic changes may suggest that her clinical presentation was due to an exacerbation of her sickle cell disease.

Conclusion

Our case highlights an unusual case of reticulated patches as the presenting sign of a patient with sickle cell disease in vaso-occlusive crisis. Due to its infrequency, atypical cutaneous presentations of sickle cell disease may be overlooked or misdiagnosed. Therefore, it is important for providers to obtain thorough medical histories to elucidate potential disease exacerbations that may require immediate treatment to minimize disease morbidity.

Potential conflicts of interest

The authors declare no conflicts of interest

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