Chronic ulcer in a patient with essential thrombocythemia taking hydroxyurea

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Abstract

Chronic skin ulcers in patients with suspected pyoderma gangrenosum can, on closer inspection and further workup, have a different cause. Recognition of key features on clinical examination such as the presence of atrophie blanche is key to avoid misdiagnosis of pyoderma gangrenosum and its subsequent treatment with high-dose corticosteroids and other immunosuppressive medications.

Keywords: atrophie blanche, livedoid vasculopathy

Introduction

The misdiagnosis of pyoderma gangrenosum (PG) exposes patients to risks associated with its treatment including immunosuppressive medications. One of the conditions that can mimic PG is vascular occlusive disease. Livedoid vasculopathy is a rare thrombo-occlusive disorder of medium-size blood vessels that results in significantly painful, slow-healing ulcers typically of the lower extremities. Prompt diagnosis of this entity by noting the clinical finding of atrophie blanche is essential to prevent misdiagnosis and delays in treatment.

Case Synopsis

An 82-year-old woman with a history of essential thrombocythemia on hydroxyurea presented to the emergency department with a one-year history of lower extremity ulcers. Although she had a prior shave biopsy of the left medial malleolus revealing traumatized seborrheic keratosis, there was no history of trauma to the right malleolus. Outpatient treatment for presumed PG with high-potency topical corticosteroids for three months and prednisone 0.5mg/kg for one month, dose limited by gastrointestinal and insomnia side effects, was insufficient at stopping ulcer progression.

She presented with two full-thickness tender ulcers on the right distal leg with notable absence of undermined or violaceous edges. On the left ankle, she had an expanding ulcer surrounded by prominent porcelain-white stellate scarring (**Figure 1A**). Given the clinical finding of atrophie blanche and history of thrombocythemia, the differential diagnosis included livedoid vasculopathy, hydroxyurea-induced ulcers, venous ulcer, PG,

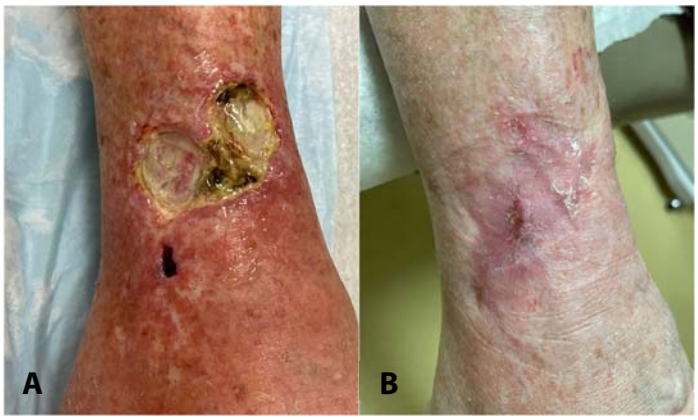

Figure 1. ***A)*** *Prominent atrophie blanche surrounding an expanding ulcer.* ***B)*** *Healed ulcer with complete re-epithelialization.*

calciphylaxis, or infection. Punch biopsy demonstrated deep fibrin thrombi and perivascular neutrophilic inflammation suggestive of vasculopathy (**Figure 2**). Tissue cultures for bacteria, fungus, and acid-fast bacilli were negative. Laboratory work-up including cANCA (cytoplasmic anti-neutrophil cytoplasmic antibody) and pANCA (perinuclear ANCA) were negative, and platelet count was elevated at 521K/μL (normal 150-400K/μL).

The likely multifactorial etiology for this patient's ulcers guided a multifaceted treatment approach. Hydroxyurea was stopped given concern for contributing to leg ulcers [1] and she was switched to anagrelide, resulting in improved control of platelet count, which had trended up into the 900K/μL range while off hydroxyurea. She started aspirin 162mg daily, pentoxifylline 400mg three times a day, and nifedipine 30mg daily. In addition, she received radiofrequency venous ablation in the right leg to treat venous reflux exhibited on ultrasound. With the above interventions, her lower extremity ulcers healed over the following three months with complete re-epithelialization (**Figure 1B**) and resolution of pain, enabling tapering off nifedipine and pentoxifylline.

Case Discussion

The clinical finding of atrophie blanche in this case was essential because it indicated a vasculopathic process, allowing initiation of treatment for livedoid vasculopathy and avoiding unnecessary further immunosuppression for PG, her previously presumed diagnosis. Because PG is a rare inflammatory skin condition that can be difficult to diagnose, the Delphi exercise established one major criterion and 8 minor criteria—of which one major and four of 8 minor criteria were established as a guideline for diagnosing PG [1]. The major criterion is biopsy of ulcer edge showing neutrophilic infiltrate and the 8 minor criteria are 1) exclusion of infection; 2) pathergy; 3) history of inflammatory bowel disease or inflammatory arthritis; 4) history of papule, pustule, or vesicle ulcerating within four days of appearing; 5) peripheral erythema, undermining border, and tenderness at ulceration site; 6) multiple ulcerations, with at least one on an anterior lower leg; 7) cribriform or "wrinkled paper" scars) at healed ulcer sites; and 8) decreased ulcer size within one month of initiating immunosuppressive medication. This patient had one major criterion (biopsy with perivascular neutrophilic infiltrate) and three minor criteria (exclusion of infection through tissue culture; possible pathergy, though the larger ulcer on her right leg was not preceded by trauma; and multiple ulcerations), therefore did not meet criteria for ulcerative PG.

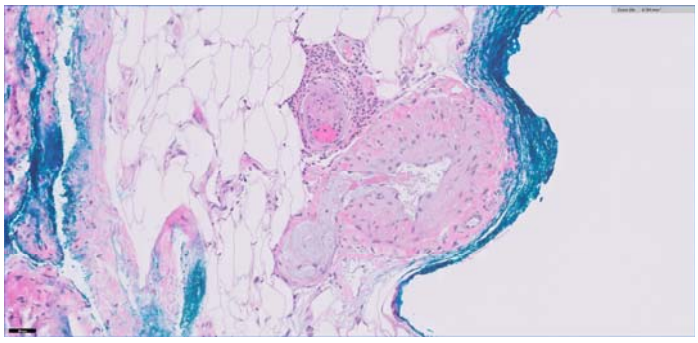

Figure 2. *Biopsy demonstrates intravascular fibrin thrombi and abundant surrounding neutrophilic inflammation. H&E, 200×.*

This patient's livedoid vasculopathy was likely driven by thrombophilia from essential thrombocythemia, leading to classic findings of atrophie blanche on the lower extremities [3,4]. Lack of response to anti-inflammatory agents such as systemic corticosteroids is also characteristic of livedoid vasculopathy and in this case was a helpful clue against the diagnosis of PG [3]. In patients with atrophie blanche, it is important to consider other etiologies and comorbid conditions including venous insufficiency, small vessel vasculitis, hypercoagulable states, or autoimmune connective tissue disease such as lupus or antiphospholipid syndrome [5] because treatment of underlying conditions together with treatments targeting vasculopathy is critical for healing these ulcers.

The most effective and common monotherapy for livedoid vasculopathy is anticoagulation with low-molecular weight heparin, warfarin, or direct oral anticoagulants [4]. This can achieve a response rate of near 100% and rivaroxaban is the most frequently used agent. Other therapies include antiplatelet

agents (aspirin, pentoxifylline, dipyridamole) and systemic corticosteroids (especially for patients with an underlying rheumatologic disorder). Other rarely reported treatments include intravenous immunoglobulin and hyperbaric oxygen therapy [6,7]. This patient's ulcers healed with increasing the dose of aspirin and the addition of pentoxifylline and nifedipine. Ultimately, there is significant clinical heterogeneity amongst patients with livedoid vasculopathy and further investigation is needed to clarify the best management approach for these complex patients.

Conclusion

We present this case to reinforce the importance of recognizing atrophie blanche on examination as a clue to vasculopathy, considering possible underlying comorbid conditions, and promptly initiating treatment to enhance blood flow and enable ulcer healing.

Potential conflicts of interest

The authors declare no conflicts of interest.

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