Thrombotic cutaneous gangrene associated with ulcerative colitis

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INTRODUCTION

Ulcerative colitis (UC) has several well-documented associated cutaneous sequelae. Pyoderma gangrenosum is most specific to UC. Other manifestations include erythema nodosum, erythema multiforme, perineal fistulas, cutaneous dermatoses, and less frequently, thrombotic cutaneous gangrene.[1,2] Thrombotic cutaneous gangrene is a particularly rare complication but has been previously associated.[1-5] As the name suggests, focal microvascular thrombosis is thought to be the etiology, secondary to a procoagulant state in this condition. On histology, microthrombi can be seen in the superficial dermis.[5] Management of these lesions is not clearly established, but the condition has previously been successfully treated with various combinations of systemic steroids, warfarin, and intravenous heparin.[1] Sulfasalazine and azathioprine have been used for relief of UC symptoms, though concomitant use with warfarin requires dosage adjustment of warfarin.[3] The goal of therapy should be early anticoagulation and prevention of progressive cutaneous infarction. Prior to beginning therapy, a thrombophilia panel and skin biopsy should be performed.[1]

UC produces a hypercoagulable state, which may be associated with the increased levels of factors Va, VIIa, VIIIa, Xia, Xa, fibrinogen, von Willebrand factor (vWF), platelets, and cryoglobulins, as well as deficiencies in antithrombin III, protein C, and protein S levels.[1,3,4,6] Endotoxin-induced coagulation, monocyte-derived tissue factors, and elevated homocysteine levels may also play a role.[3,7,8] The hypercoagulable state during an active flare of UC is posited to result primarily from elevated platelets and vWF.[6] Of note, the elevated vWF levels may result from vascular injury secondary to bowel inflammation or an acute phase response to endothelial cell stimulation by mediators released during the inflammatory process.[6] Despite the clear imbalances in hemostasis and the connection with inflammatory bowel disease, the underlying mechanism behind the hypercoagulable state in UC remains unclear.[9]

Abbreviations used:

vWF: von Willebrand factor
UC: ulcerative colitis

Possible mechanisms of thrombotic cutaneous gangrene include necrotizing cutaneous vasculitis induced by circulating antigen-antibody complexes, arterial and venous occlusions, capillary and venous thrombosis, and cryofibrinogenemia with thrombosis of blood vessels.[4] Patients with UC often have significantly elevated markers of hypercoagulability, including thrombin-antithrombin complex, prothrombin fragments 1 and 2, and D-dimers when compared to patients without UC. However, patients with active UC did not differ significantly from those with inactive UC. Thus, it can be inferred that patients with UC are in a chronic low-grade hypercoagulable state.[10] However, treatment with anticoagulation in the setting of thromboembolic events balanced against the risks of hemorrhagic bleeding is the standard of care.[3]

CASE REPORT

A 38-year-old white male with a history of uncontrolled UC presented after a rash on his

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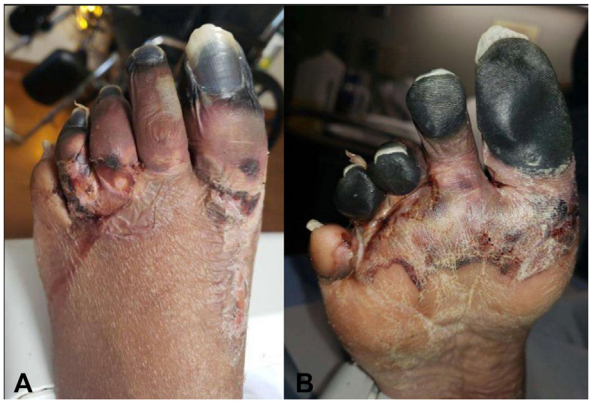

Fig 1. Left foot with both dorsal (**A**) and plantar (**B**) views showing necrotic toes with *black* eschars and areas of desquamation.

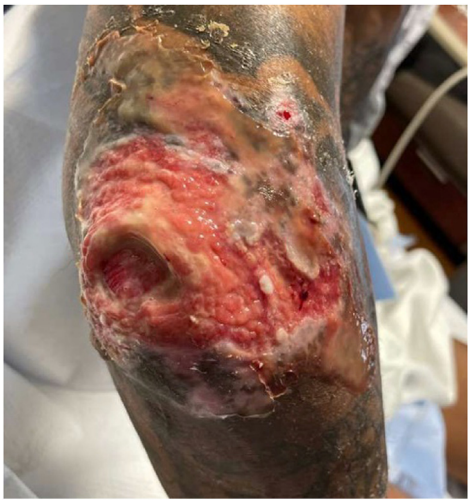

Fig 2. The right elbow with deep ulcers with muscle exposed and desquamation.

feet, arms, and legs, which began 2 weeks prior. He was initially admitted to an outside facility for shortness of breath and anemia resulting from hematochezia; while there he developed painful hemorrhagic bullae with areas of necrosis on his elbows and feet. He was treated with intravenous steroids, which improved his shortness of breath and bloody diarrhea without alleviating the rash. The lesions on the skin progressed to deep ulcers and in some of them frank necrotic areas with black eschars (Figs 1 and 2).

A biopsy of representative areas of the rash on the feet revealed intravascular thrombi, extravasated red blood cells, and early epidermal necrosis (Fig 3). A further coagulation panel was conducted, showing that the factor V, JAK2, glycoprotein 2b, cryoglobulins, and platelet levels were all within normal limits. He was found to have normal C4 levels and elevated C3 levels. While proteinase antibodies were elevated, the remainder of an autoimmune panel, including lupus anticoagulant, was negative. Additionally, he was found to have a decreased partial thromboplastin time, normal prothrombin time and international normalized ratio, and elevated antithrombin III, protein C/S activity, fibrinogen, erythrocyte sedimentation rate, and C-reactive protein. At the outside facility, he was noted to be anemic with a hemoglobin of 9.9, which persisted throughout his disease course.

Prior to this episode, the patient's only medications were iron supplements, mesalamine, and loperamide. Once evaluated, the patient was initiated on amlodipine 10 mg which was titrated up to 20 mg daily to increase distal perfusion to the toes. He was concurrently being treated with apixaban to promote anticoagulation. Intravenous steroids were continued to control his UC, in combination with mesalamine, and an infliximab infusion was started while in the hospital.

While some reperfusion of his distal extremities was achieved, multiple amputations were still required because of ongoing necrosis to prevent further and worsening infection.

DISCUSSION

After eliminating other possible etiologies of a hypercoagulable state, the most likely cause for thrombotic gangrene in this patient was his UC. The concurrence of the patient's flare of bloody diarrhea, followed shortly thereafter by the presence of the necrotic rash, further supports the relationship between the 2. His subsequent laboratory workup suggests that his hypercoagulability is likely rooted in the extrinsic coagulation pathway, as evidenced by his decreased partial thromboplastin time. One such possible explanation is that UC can lead to elevated levels of vWF, which help to stabilize and prolong the half-life of factor VIII. Additionally, vWF can mediate platelet-to-platelet interactions and platelet adhesion to the subendothelium, thus promoting thrombogenesis.[6]

In patients presenting with evidence of early necrosis or ischemia, dermatologists need to investigate any history of UC or other hypercoagulable diseases. Basic workup includes coagulation studies and hypercoagulable panels, as well as a biopsy of the afflicted area. Once the diagnosis is established, the goal of therapy should be early anticoagulation and the prevention of progressive cutaneous infarction. This can potentially be achieved using a combination of vasodilators, such as amlodipine, to improve distal perfusion, as well as an anticoagulant to prevent further thrombi formation. Lastly, intravenous steroids and other therapies can be used to

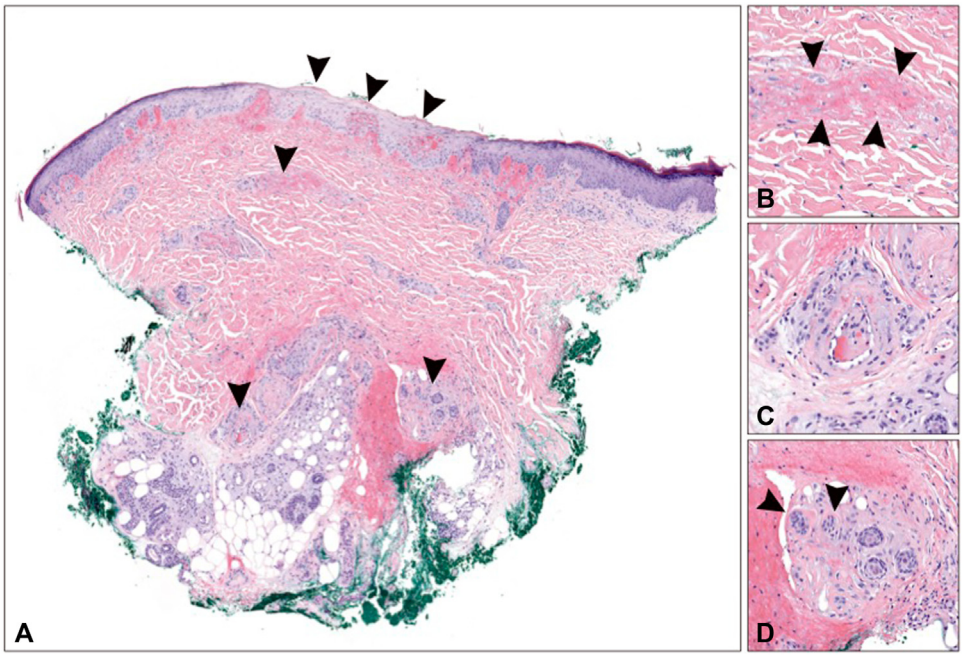

Fig 3. Histology from a punch biopsy of the left knee shows mild acanthosis and superficial perivascular and periadnexal lymphocytic infiltrate. **A,** Toward the edge of the skin punch, there is focal edematous stroma and extravasated erythrocytes. There is mild acanthosis, focal epidermal necrosis, and extravasated erythrocytes within the papillary dermis. In addition, a separated layer of full-thickness necrotic epidermis is present in the overlying crust. **B,** Within the superficial dermis, multiple necrotic vascular remnants with intraluminal thrombi and associated extravasated erythrocytes are present. **C,** In the deeper dermis, a few occluded vessels with evidence of thrombosis and recanalization are seen. **D,** Few adjacent eccrine coil segments show evidence of necrosis.

control distal inflammation as well as the UC flare. However, it is still unclear whether controlling the UC flare should remain a priority in treatment as there is limited data to suggest whether thromboembolic events favor the active or quiescent phases of the disease.[10]

Conflicts of interest

Dr Correa-Selm is a consultant for AccuTec Blades and Novartis pharmaceutical. The other authors have no conflicts of interest to declare.

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