

CHALLENGE CASES

Evolving bullous lesions in a patient with May-Thurner Syndrome

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Abstract

The diagnosis and treatment of cutaneous lesions can be challenging in cases where skin lesions undergo evolution. Here we present a complicated case in which histopathologic findings evolved over the course of the disease, reflected through different discoveries in multiple biopsy specimens. This case highlights the importance of correlating clinical history and presentation with histologic findings to obtain the correct diagnosis in dermatologic diseases.

Case Presentation

A 16-year-old male presented to the dermatology clinic with a four month history of progressively worsening pruritic blisters on bilateral lower extremities. Past medical history included a recent diagnosis of May-Thurner Syndrome with extensive deep venous thrombosis of the legs, managed with aspirin, low-molecular-weight heparin, and trimethoprim-sulfamethoxazole (TMP-SMX). Physical exam was notable for tense blisters and bullae on the plantar feet, dorsal feet, and lower legs, with some associated overlying crust and hyperpigmentation (Figure 1A). Punch biopsies of one blister edge for histologic evaluation and perilesional skin for direct immunofluorescence (DIF) were obtained. Histology showed impressive intraepidermal collections of neutrophils along with acantholysis. DIF was positive for granular deposition of IgG along the basement membrane and intercellular deposition of IgA and C3 (Figures 1B, 1C). Laboratory values were notable for mild anemia (Hgb 10.6 g/dL) and peripheral eosinophilia (11% of differential). A basic metabolic panel was within normal limits.

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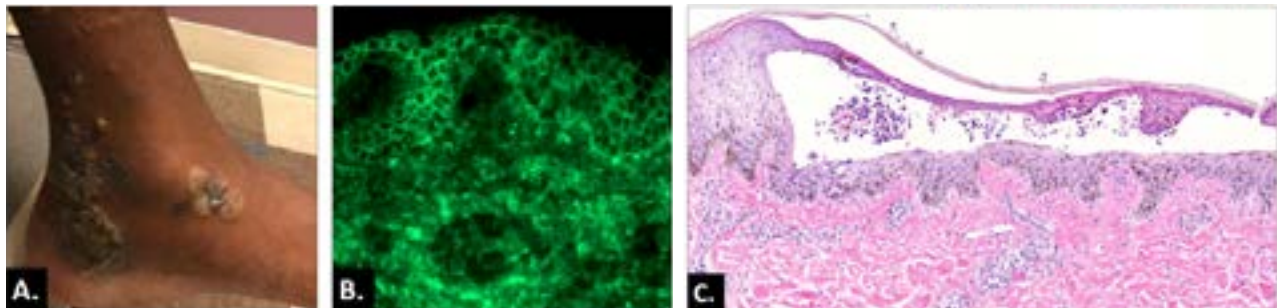


Figure 1. (A) Annular bullae with scattered pustules at the periphery on the medial ankle (B) Positive deposition of IgA in an intercellular pattern (C) Acanthosis and intraepidermal collections of neutrophils

Challenge Question 1: Based on the patient's history, clinical presentation, and histologic findings, what is the most likely diagnosis?

- A. Bullous lupus erythematosus
- B. Bullous drug eruption secondary to TMP-SMX
- C. Epidermolysis bullous acquisita
- D. Bullous pemphigoid
- E. Bullous arthropod bite reaction

Based on clinical presentation and histopathologic findings, the patient was diagnosed with bullous lupus erythematosus (answer choice A) and started on methotrexate 10mg weekly. Despite therapy, lesions evolved into hypertrophic, verrucous plaques at sites of prior blisters (Figure 2A). A punch biopsy was obtained from a vegetative plaque which demonstrated acanthosis, papillomatosis, and hyperkeratosis of the epidermis with intraepidermal collections of neutrophils and eosinophils, without significant acantholysis. Within the dermis, there was an inflammatory infiltrate composed of lymphocytes, neutrophils, and eosinophils (Figure 2B). Additional serologic workup revealed negative ANA and normal complement levels. During this time, he also developed abdominal pain and diarrhea. Stool studies were negative for occult blood but notable for significantly elevated calprotectin levels. Tissue transglutaminase antibodies were negative.

Challenge Question 2: Given this additional information, what is the most likely diagnosis?

- A. Bullous systemic lupus erythematosus (SLE)
- B. Dermatitis herpetiformis associated with celiac disease
- C. IgA pemphigus with features of pemphigus vegetans
- D. Bullous drug eruption
- E. Bullous pemphigoid

This patient's skin disease was ultimately diagnosed as a vegetative presentation of IgA pemphigus (answer choice C). IgA pemphigus is a rare autoimmune blistering disorder that can demonstrate variable clinical findings. This patient's clinical presentation and skin biopsies are challenging because they displayed features of three different diseases that can have overlapping findings: IgA pemphigus, pemphigus vegetans, and pyodermatitis vegetans (summarized in Table 1).

IgA pemphigus is typically characterized by the intertriginous distribution of vesicles and pustules, often in an annular configuration. The diagnosis is usually confirmed by positive



Figure 2. (A) Verrucous hyperkeratotic plaques on the medial ankle, at sites of prior bullae (B) Intraepidermal neutrophils with acanthosis and no evidence of acantholysis

IgA deposition on the cell surface of keratinocytes.¹ Pemphigus vegetans, which is a rare variant of pemphigus vulgaris, is characterized by vegetative plaques in areas of prior blisters and erosions.² Pemphigus vegetans most often affects the intertriginous sites, scalp, and face, but may be a response to chronic and treatment-resistant lesions of pemphigus vulgaris.³ Direct immunofluorescence studies will show deposition of IgG and C3 in an intercellular pattern and occasionally along the epidermal basement membrane.⁴ Pyodermatitis vegetans is a chronic mucocutaneous dermatosis, considered on the spectrum of neutrophilic dermatoses. It is strongly associated with inflammatory bowel disease (IBD) and manifests as papules and pustules which coalesce to form vegetating plaques. The majority of patients with pyodermatitis also have oral mucosal involvement, termed pyostomatitis. Direct immunofluorescence is usually negative, although in some cases, nonspecific positive findings have been reported, including deposition of C3, IgG, and IgA either along the basement membrane zone or at intercellular spaces of the epidermis.

Case Findings	Pyodermatitis	Pemphigus Vegetans	IgA Pemphigus
Large bullae formation		X	
Vegetative verrucous plaques	X		
Intraepidermal neutrophils	X	X	X
Epidermal acanthosis, papillomatosis with intraepidermal eosinophils	X	X	
DIF IgA intercellular			X
DIF IgG along basement membrane		X	
Association with Crohn's disease	X		X
Lack of mucosal involvement			X
Peripheral eosinophilia	X		

Table 1. Clinical presentation and histologic findings in pyodermatitis, pemphigus vegetans, and IgA pemphigus

Challenge Question 3: What additional work-up would be beneficial in this patient's case?

- A. ELISA for BP180 antigen
- B. Anti-neutrophil cytoplasmic antibodies
- C. Colonoscopy with esophagogastroduodenoscopy
- D. PET/CT scan

The patient underwent colonoscopy and esophagogastroduodenoscopy (EGD) (answer choice C), which revealed pan-colitis from the terminal ileum to the cecum. He was subsequently diagnosed with Crohn's disease and started on infliximab and prednisone, in addition to methotrexate. IBD has been associated with many different cutaneous manifestations. Some associated dermatoses are common and easily recognizable such as psoriasis, pyoderma gangrenosum, and hidradenitis suppurativa, while others are rare.

Discussion

Our patient's case was unusual and complicated in that the clinicopathologic findings did not neatly fit any single diagnosis. We hypothesize that his skin disease was likely

unrelated to his medications or medical history of May-Thurner syndrome (a red herring). Rather, his inflammatory bowel disease may have triggered an immunologic response that led to the development of his cutaneous disease. Despite the initial biopsy and immunofluorescence findings, the patient's case in its entirety did not fit the diagnosis of lupus erythematosus. The patient's presentation of large vegetative plaques in areas of prior blister formation and diagnosis of Crohn's disease ultimately led to a diagnosis of IgA pemphigus with features of pemphigus vegetans (Q2, answer choice C). Treatment of this disease involves the use of immunosuppressive medications and controlling any pertinent underlying systemic illness such as Crohn's disease. At this time, the patient remains on infliximab infusions every six weeks for his Crohn's disease, along with methotrexate 12.5mg weekly. His prednisone has been slowly tapered down to 10mg daily with no recurrence of his blisters or the verrucous plaques.

Conclusion

In many specialties, pathology is relied upon to make final and definitive diagnoses. Diseases of the skin can be challenging as similar pathologic findings can be seen in different

entities, different pathologic findings can be seen within the same disease, and skin biopsies can be non-specific. Thus, focusing on both clinical and pathologic information is key to diagnosing complex cutaneous diseases. Additionally, treatment of primary diseases that drive cutaneous disease must be taken into consideration. In this case, large vegetative plaques in areas of prior blister formation with concurrent Crohn's disease led to the diagnosis of IgA pemphigus. Treating both the dermatologic disease and underlying IBD led to resolution of the verrucous plaques.

Disclosures

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