Concomitant pemphigus herpetiformis and sarcoidosis

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INTRODUCTION

Pemphigus herpetiformis (PH) is a rare variant of pemphigus and accounts for approximately 7% of cases.[1] PH combines the clinical features of dermatitis herpetiformis with the histologic features of pemphigus. Clinically, the plaques are herpetiform or even annular.[1] PH follows a more benign course with mild skin disease and no mucosal involvement. The histopathology findings can be subtle with minimal to absent acantholysis and a mixed infiltrate of eosinophils and neutrophils.[1] Biopsies, direct immunofluorescence, indirect immunofluorescence, and serum autoantibodies are required to make the diagnosis. Autoantibodies to desmoglein (Dsg) 1 are common, although Dsg3 and desmocollin 1 have been reported.[2] We present a rare case of the simultaneous onset of PH and sarcoidosis.

Abbreviations used:

Dsg:	desmoglein
H&E:	hematoxylin-eosin
IL:	interleukin
PH:	pemphigus herpetiformis

CASE REPORT

A previously healthy 44-year-old white woman had an acute-onset pruritic rash and shortness of breath. The initial outside workup included a computed tomography scan of the chest that showed axillary and mediastinal adenopathy. The patient underwent axillary and mediastinal lymph node sampling that showed noncaseating granulomas, negative bacterial and fungal cultures, and a polyclonal lymphocyte population. Results of extensive blood work were negative for infection or malignancy. At follow-up with pulmonology, the patient's shortness of breath had improved; however, her pruritic rash was unchanged, and she was referred to the dermatology department.

The physical examination was remarkable for multiple, moderately well-marginated pink, herpetiform, and annular plaques with a collarette of scale distributed along the abdomen and chest (Fig 1, *A* and *B*). There was a predilection to areas of friction and prior surgical scars. Punch biopsies for hematoxylin-eosin (H&E) staining and direct immunofluorescence were performed. The H&E slides showed a spongiotic reaction pattern with mild perivascular lymphocytic and eosinophilic dermal inflammation (Fig 2, *A*), and the direct immunofluorescence showed a strong intercellular pattern of IgG and C3 (Fig 2, *B*). Indirect immunofluorescence was positive on monkey esophagus at a titer of 1:80. Enzyme-linked immunosorbent assay showed an elevated Dsg3 antibody of 183 (abnormal >9) and a normal Dsg1. Based on the clinical and histopathologic features, PH was diagnosed.

The patient was re-evaluated by the pulmonology department and was found to have persistent mediastinal adenopathy, an elevated angiotensin-converting enzyme level, and a normal infectious workup. Primary pulmonary sarcoidosis was diagnosed. The pulmonary and skin diseases improved with inhaled and topical corticosteroids, respectively. Her skin worsened within 1 year of follow-up and required oral minocycline; her sarcoidosis remained stable.

DISCUSSION

We report a rare case of sarcoidosis co-occurring with PH that displayed an excellent response to topical corticosteroids and oral minocycline. Unlike

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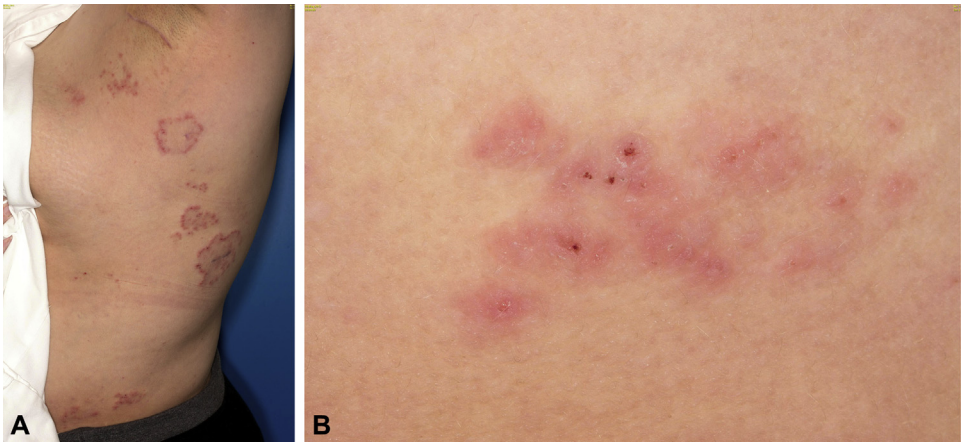

Fig 1. Pemphigus herpetiformis. **A**, Multiple moderately well-marginated pink, herpetiform, and annular plaques with a collarette of scale distributed along the abdomen and chest. **B**, Close-up photograph of the same lesions.

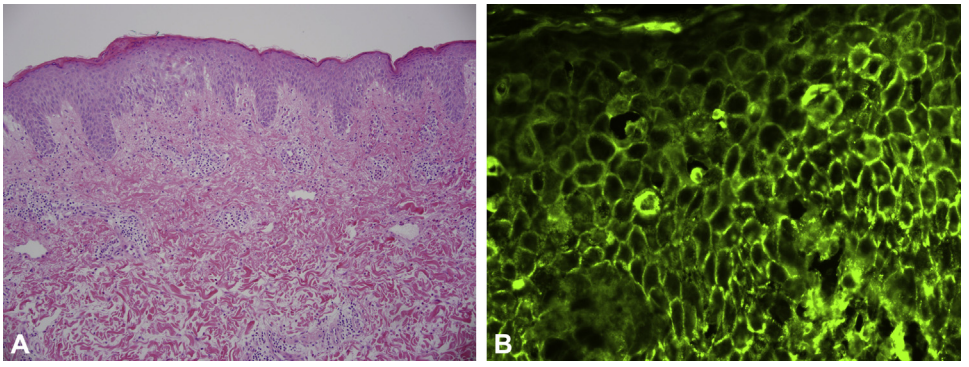

Fig 2. **A**, H&E staining shows spongiotic reaction pattern with eosinophils, mild perivascular lymphocytic infiltrate, and eosinophilic dermal inflammation. **B**, IgG direct immunofluorescence showed a strong intercellular, "lace-like" pattern of IgG. (Original magnifications **A**, ×100; **B**, ×40.)

other forms of pemphigus, PH often responds to topical corticosteroids and oral antibiotics.[1] The close time proximity and correlated disease severity suggests that these diseases may be related to each other. It is possible that in a genetically prone individual, the inflammatory milieu of acute sarcoidosis may be permissive for the development of PH. The pathogenesis of pemphigus is incompletely understood but is thought to be driven by a T helper 2 cytokine response secondary to pathogenic B cells.[3] In comparison, sarcoidosis is a T helper 1–driven process with up-regulation of tumor necrosis factor-α, interleukin (IL)-12, IL-15, IL-18, and macrophage inflammatory protein-1.[4] Although the pathogenesis of PH and sarcoidosis are different, there is emerging evidence that IL-8 and p38 may play a key role in cell recruitment and signaling in both diseases.

Multiple chronic inflammatory disorders have increased IL-8 activity; these include PH, sarcoidosis, psoriasis, and palmoplantar pustulosis.[5-7] IL-8 is a neutrophil chemotactic factor. In PH, the up-regulation of IL-8 on keratinocytes drives the recruitment of neutrophils, which degranulate and lead to blister formation.[6] IL-8 levels are elevated in patients with active, pulmonary sarcoidosis.[7] Phosphorylation of p38 also plays a critical role in the intracellular signaling cascade of multiple inflammatory diseases; these include PH, sarcoidosis, and psoriasis.[8-10] Patients with sarcoidosis have higher basal activity and increased phosphorylation of p38; which may lead to inflammation.[9] Anti-Dsg3 antibodies trigger intracellular signaling in keratinocytes. This signaling leads to the phosphorylation of p38 and subsequent apoptolysis.[10] Therefore, the cytokine milieu of an active sarcoidosis with increased IL-8 levels and phosphorylation of p38 may be permissive for development of PH in someone harboring anti-Dsg antibodies. A clear associative or causal relationship between PH and

sarcoidosis is not apparent based on our current understanding of these 2 diseases. However, rare co-occurrences of diseases can provide unique insight into possible pathogenic drivers such as IL-8 upregulation and p38 signaling.

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