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Authors
Amber, Kyle T
Valdebran, Manuel
Lu, Yuxin
et al.

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Localized pretibial bullous pemphigoid arising in a patient on pembrolizumab for metastatic melanoma.

Kyle T. Amber[1], **Manuel Valdebran**[1], **Yuxin Lu**[2], **Sebastien De Feraudy**[1], and **Kenneth G. Linden**[1]

[1]Department of Dermatology, University of California Irvine, Irvine, California, USA.

[2]Department of Pathology, University of California Irvine Medical Center, Orange, California, USA.

To the editors,

An 82-year-old female presented with a pruritic bullous dermatitis to the bilateral pretibial legs of 5 months duration. Her medical history was significant for metastatic melanoma Stage IV (T1N2M1b) for which she had been placed on pembrolizumab 6 months prior to the onset of her pretibial rash due to the development of widespread nodal involvement and pulmonary nodules. She received 9 doses of 2mg/kg at approximately 3 week intervals, with a significant decrease in the size of her lung nodules prior to developing her pretibial rash. The plaque had begun as a faint pruritic erythematous patch, for which the patient tried numerous therapies including topical neomycin and other over-the-counter topical antibiotics. Thus, contact dermatitis was originally suspected, and the patient was instructed to discontinue all therapies. Her dermatitis progressed, with subsequent development of tense bullae and erosions at the site of previous bullae on an erythematous plaque limited to her pretibial legs (Figure 1).

Histopathology of an intact vesicle demonstrated a subepidermal split with numerous eosinophils (Figure 2a). Perilesional direct immunofluorescence demonstrated strong binding of C3 and IgG at the basement membrane zone (Figure 2b). Indirect immunofluorescence demonstrated IgG deposition at a titer of 1:1280 on monkey esophagus substrate, with a positive epidermal pattern at a titer of 1:2560 on human split-skin substrate. Testing for IgA was negative. ELISA for BP180 was positive at 46 units, but BP230 was negative at 2 units, with a reference of less than 9 for both tests. In combination, these findings supported the diagnosis of localized pretibial bullous pemphigoid, a grade 1 adverse event to pembrolizumab. The patient was subsequently placed on topical clobetasol to the affected areas twice daily while continuing on pembrolizumab for her metastatic melanoma. She developed a transient generalization of her bullous pemphigoid which responded to a 2-week prednisone taper. Thereafter, she had limited pretibial involvement which was controlled with clobetasol at 6-months follow-up.

Address correspondence to: Dr. Kyle T. Amber, Department of Dermatology, University of California Irvine Health, 118 Med Surg 1, Irvine, CA 92697, P 305-609-2110: F: 949-824-7454, KAmber@UCI.edu.

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Bullous pemphigoid is an autoimmune subepidermal blistering disorder characterized by subepidermal bullae formation, deposition of immunoglobulins or complement components at the dermoepidermal junction (DEJ), and autoantibodies against the BP180 and/or BP230. BP presents typically in elder individuals with a phase of pruritus followed by widespread blister formation. Less common variants have been described and include vesicular pemphigoid, pemphigoid vegetans, localized pretibial pemphigoid, and pemphigoid nodularis [1]. Our patient presented with localized pretibial pemphigoid, a rare variant of BP, reported in approximately 1% of BP patients [2]. While clinically distinct, it is indistinguishable serologically and histopathological from the widespread variant BP [3, 4].

PD-1 inhibitor induced BP has been described previously in several patients [5–7]. It is thought that the result of blocking the PD-1/PD-L1 axis leads to a breakdown of tolerance and a development of a T cell response against BP 180 [6, 8]. On the other hand, Naidoo et al propose the coexistence of a humoral response through a B-cell germinal center stimulation by $PD1^+$ follicular helper T cells [6].

Recent studies have suggested a potential relation between melanoma and BP, though this has yet to be confirmed in large population studies. Investigators have demonstrated the expression of BP180 in melanoma cells but not in normal melanocytes [9]. Likewise, several cases have demonstrated a parallel with clinical course of BP and melanoma [10]. Moreover, the HLA-DQB1*03:01 allele which has been associated to BP has been found in higher frequencies in melanoma patients [11]. Thus, patients receiving PD-1 inhibitors for melanoma may be both exposed to BP180 from their melanoma, as well as experience T-cell dysregulation leading to functional autoimmunity against the BP180 protein [12].

We herein present, to our knowledge, the first reported case of localized bullous pemphigoid arising in a patient receiving PD-1 inhibitors. This case further supports the systemic nature of localized pretibial BP. It remains unclear why some patients develop this localized form rather than generalized, despite the systemic circulation of autoantibodies.

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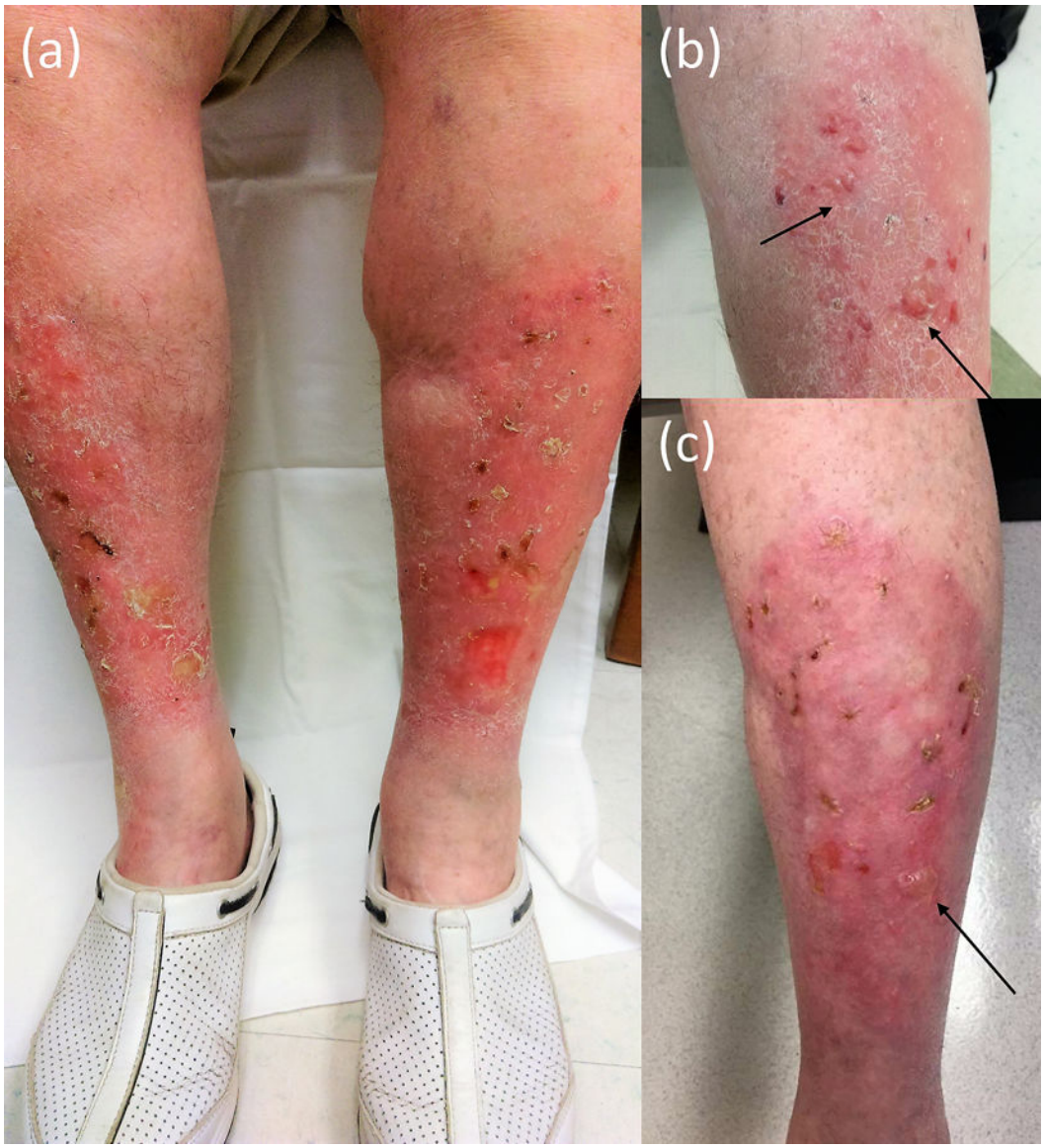

Figure 1.

Tense bullae and erosions at the site of previous bullae on an erythematous plaque limited to the pretibial legs on presentation (a), and follow up (b,c). Arrows point to few residual tense bullae

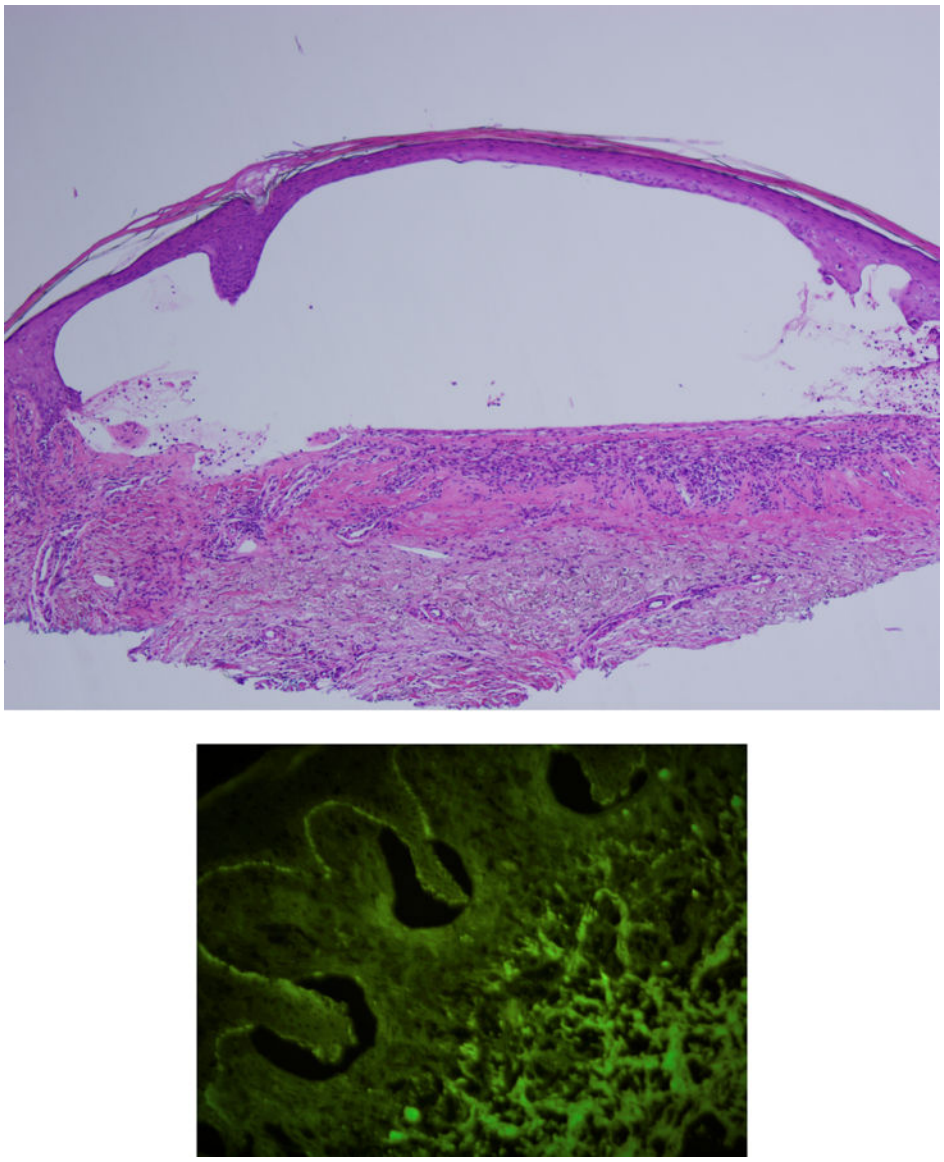

Figure 2.

A) hematoxylin and eosin stained tissue demonstrating subepidermal clefting with numerous eosinophils (10x) and C) confirmation of linear IgG along the basement membrane by direct immunofluorescence.