Published in final edited form as:

Melanoma Res. 2017 February ; 27(1): 65–67. doi:10.1097/CMR.0000000000000307.

A case report of bullous pemphigoid associated with a melanoma and review of the literature

Kyle T. Amber, Christine M. Panganiban, Dorota Korta, Sebastien de Feraudy, Kristen M. Kelly, and Sergei A. Grando

Department of Dermatology, University of California Irvine, Irvine, California, USA

Abstract

The association of bullous pemphigoid with melanoma remains controversial and poorly understood. Recent studies report the presence of the bullous pemphigoid antigen, BP180, in melanoma cells, yet not normal melanocytes, suggesting an underlying mechanism for cases of melanoma-associated bullous pemphigoid. We report on an 88-year-old woman who showed a temporal relationship between the development of bullous pemphigoid and melanoma. The patient did not receive programmed death ligand 1 inhibitor therapy and improved rapidly following complete excision of her melanoma, with clobetasol, doxycycline, and niacinamide. We review the literature on the relationship between bullous pemphigoid and melanoma, and propose a mechanism underlying a melanoma-associated bullous pemphigoid.

Keywords

BP180; bullous pemphigoid; collagen XVII; epitope spreading; melanoma

Case

An 88-year-old woman initially presented for evaluation of a pruritic rash. Review of her previous medical history was notable for breast cancer treated by radical mastectomy as well as the following medications: tolterodine, propranolol, and a multivitamin. On skin exam, she had multiple pink papules on both thighs and erythema and excoriations on her back. There were no blisters noted at initial presentation. During the full skin exam, a pigmented lesion was noted on her clitoral hood. The patient stated that this had been present for an unknown period of time, but that she had noted growth over the course of 4 months. Clinical suspicion was high for melanoma and an excisional biopsy of the 1 cm lesion was performed on the day of presentation, indicating a spitzoid melanoma with a depth of 0.75 mm and numerous mitoses (Fig. 1). Lateral margins were positive for melanoma *in situ*.

One week following the biopsy, the patient returned to clinic for follow-up of the pruritic rash, which was progressing. On physical exam, she still had multiple pink papules on the

Correspondence to Kyle T. Amber, MD, Department of Dermatology, UC Irvine Health, 118 Med Surg 1, Irvine, CA 92697-2400, USA, Tel: + 1 305 609 2110; fax: + 1 949 824 7454; kamber@uci.edu.

Conflicts of interest

There are no conflicts of interest.

legs, as well as erythema and excoriations on her back with few small tense bullae. A biopsy was performed from a characteristic lesion. She was started on triamcinolone for symptomatic relief while awaiting biopsy results.

Pathology indicated vacuolar interface changes, mild spongiosis, and clusters of junctional eosinophils. Indirect immunofluorescence was subsequently performed, showing immunoglobulin G antibodies to the basement membrane zone with a titer of 1 : 1280 on monkey esophagus and epidermal binding on salt-split skin. Indirect immunofluorescence for immunoglobulin A antibodies was negative. Enzyme-linked immunosorbent assay for anti-BP180 and anti-BP230 antibodies were 41 and 10, respectively, with a reference range below 9. Together, these findings were consistent with a diagnosis of bullous pemphigoid.

Treatment of bullous pemphigoid in this patient was started with clobetasol ointment. Several days later, she underwent wide excision of the melanoma with a negative sentinel lymph node biopsy. Because of the significant surgery and concerns for poor wound healing, systemic corticosteroids were avoided, and niacinamide 500 mg thrice daily and doxycycline 100 mg twice daily were added. Within 2 weeks, her lesions had resolved almost completely and she did not develop new bullae. This treatment regimen was continued for 5 months, during which time she did not develop any new lesions nor experience significant pruritus.

Discussion

The association of bullous pemphigoid with melanoma remains poorly understood. Cases of new-onset bullous pemphigoid in association with melanoma have been described previously [1–4]. The reported cases as well as the present case are summarized in Table 1. Bullous pemphigoid is associated with autoantibodies to the BP180 and BP230 antigens. Interestingly, a recent study reported expression of the endodomain of BP180 in malignant melanoma; this is absent in benign melanocytic tumors [5]. BP230 is additionally expressed in melanoma cell lines as well as normal human melanocytes [6]. Shimbo *et al.* [6] reported a significantly higher level of anti-BP230 antibodies in the serum of melanoma patients compared with healthy controls; however, this was not replicated in a later study [7].

Several clues point toward a direct relationship between bullous pemphigoid and melanoma. Human leukocyte antigen (HLA) polymorphisms may predispose patients to both bullous pemphigoid and melanoma. HLA-DQB1*03:01 has been noted to have a significantly higher frequency in Caucasian patients with melanoma [8]. Besides being an independent risk factor for the development of melanoma recurrence or metastasis [9], it has been noted to strongly interact with BP180 and is thus far the best-described HLA allele associated with bullous pemphigoid [10].

There additionally appears to be a temporal relationship between the clinical course of bullous pemphigoid and the patients' melanoma status. In previously reported cases, acute flares paralleled the discovery of metastatic disease [1,2,4]. In addition, as in our patient, the development of bullous pemphigoid occurred in close association with the discovery of a melanoma [1–3]. Similarly, following resection of the initial melanoma and later of an involved lymph node, Marks [1] noted a parallel improvement in their patient's bullous

pemphigoid. Following lymph node resection, the patient was able to be weaned from 60 mg of prednisone to 2.5–5 mg. Our patient experienced a significant improvement following excision of her melanoma. However, it cannot be ruled out that a combination of doxycycline and niacinamide with topical clobetasol treatment as needed was sufficient to control the patient's disease.

A similar relationship with bullous pemphigoid has been noted in neurologic disease. Up to 50% of patients with bullous pemphigoid have a neurologic disease and a strong association between the two conditions has been noted [11]. BP180 – the target of autoimmunity in bullous pemphigoid – is expressed widely in the brain [12–14] and it has been proposed that self-immunization secondary to central nervous system disease accounts for the bullous pemphigoid–neurologic disease association. Yet, Recke *et al.* [15] failed to find antibasement membrane antibodies in a cohort of patients with Parkinson's disease and multiple sclerosis. The study by Recke *et al.* [15] was, however, underpowered to compare the true prevalence of autoantibodies in patients with central nervous system disease versus the healthy population. Significantly elevated levels of nonskin binding antibodies targeting neuronal BP180 are, however, found in patients with Parkinson's disease. This suggests that sensitization to neuronal BP180 initiates an immune response, which, in only rare cases, progresses to the development of autoantibodies reacting to cutaneous domains of BP180, presumably because of an epitope spreading phenomenon [14].

Numerous cases of bullous pemphigoid and other immunobullous disease have been reported with the therapeutic use of antibodies targeting the cell death receptor 1 [programmed death ligand 1 (PD-1) inhibitors] for melanoma [16–19]. PD-1 normally functions as an immune checkpoint, preventing the activation of T-cells and promoting self-tolerance. Once inhibited, there is a higher likelihood of development of autoimmune phenomena. Should an underlying relationship between melanoma and blood pressure exist, PD-1 inhibitors would exacerbate this through loss of self-tolerance.

Much is yet to be discovered in terms of bullous pemphigoid and its association with underlying non-dermatologic diseases. We postulate that in a susceptible individual, such as one with HLA susceptibility or an intrinsically decreased self-tolerance, tumor surveilling lymphocyte infiltration into the melanoma may lead to exposure of an otherwise immune privileged protein with subsequent development of autoimmunity. The use of antibodies inhibiting PD-1 may further exacerbate this through loss of self-tolerance. Thus, the melanoma itself may contribute toward the development of bullous pemphigoid. Future studies of the incidence of melanoma in blood pressure patients compared with age-matched controls would be beneficial in determining a relationship.

References

1. Marks JM. Pemphigoid with malignant melanoma. *Proc R Soc Med.* 1961; 54:225–226. [PubMed: 19994097]
2. Parsons RL, Savin JA. Pemphigoid and malignancy. *Br J Cancer.* 1968; 22:669–672. [PubMed: 5705137]
3. Parimi LR, Chen M, Liu H, Zhang F. Bullous pemphigoid with malignant melanoma. *Indian J Dermatol Venereol Leprol.* 2015; 81:625–626. [PubMed: 26515849]

4. Beck KM, Dong J, Geskin LJ, Beltrani VP, Phelps RG, Carvajal RD, et al. Disease stabilization with pembrolizumab for metastatic acral melanoma in the setting of autoimmune bullous pemphigoid. *J Immunother Cancer*. 2016; 4:20. [PubMed: 27096097]
5. Krenacs T, Kiszner G, Stelkovics E, Balla P, Teleki I, Nemeth I, et al. Collagen XVII is expressed in malignant but not in benign melanocytic tumors and it can mediate antibody induced melanoma apoptosis. *Histochem Cell Biol*. 2012; 138:653–667. [PubMed: 22688676]
6. Shimbo T, Tanemura A, Yamazaki T, Tamai K, Katayama I, Kaneda Y. Serum anti-BPAG1 auto-antibody is a novel marker for human melanoma. *PLoS One*. 2010; 5:e10566. [PubMed: 20479946]
7. Gambichler T, Scheitz R, Hoxtermann S. Serum anti-BPAG1 autoantibody level is not a useful biomarker for cutaneous melanoma. *Melanoma Res*. 2016; 26:88–89. [PubMed: 26301970]
8. Lu M, Thompson WA, Lawlor DA, Reveille JD, Lee JE. Rapid direct determination of HLA-DQB1 * 0301 in the whole blood of normal individuals and cancer patients by specific polymerase chain reaction amplification. *J Immunol Methods*. 1996; 199:61–68. [PubMed: 8960099]
9. Bateman AC, Turner SJ, Theaker JM, Howell WM. HLA-DQB1*0303 and *0301 alleles influence susceptibility to and prognosis in cutaneous malignant melanoma in the British Caucasian population. *Tissue Antigens*. 1998; 52:67–73. [PubMed: 9714476]
10. Budinger L, Borradori L, Yee C, Eming R, Ferencik S, Grosse-Wilde H, et al. Identification and characterization of autoreactive T cell responses to bullous pemphigoid antigen 2 in patients and healthy controls. *J Clin Invest*. 1998; 102:2082–2089. [PubMed: 9854043]
11. Brick KE, Weaver CH, Savica R, Lohse CM, Pittelkow MR, Boeve BF, et al. A population-based study of the association between bullous pemphigoid and neurologic disorders. *J Am Acad Dermatol*. 2014; 71:1191–1197. [PubMed: 25174542]
12. Seppanen A, Suuronen T, Hofmann SC, Majamaa K, Alafuzoff I. Distribution of collagen XVII in the human brain. *Brain Res*. 2007; 1158:50–56. [PubMed: 17555727]
13. Taghipour K, Chi CC, Vincent A, Groves RW, Venning V, Wojnarowska F. The association of bullous pemphigoid with cerebrovascular disease and dementia: a case–control study. *Arch Dermatol*. 2010; 146:1251–1254. [PubMed: 21079062]
14. Messingham KA, Aust S, Helfenberger J, Parker KL, Schultz S, McKillip J, et al. Autoantibodies to collagen XVII are present in Parkinson's disease and localize to tyrosine-hydroxylase positive neurons. *J Invest Dermatol*. 2016; 136:721–723. [PubMed: 27015458]
15. Recke A, Oei A, Hubner F, Fechner K, Graf J, Hagenah J, et al. Parkinson's disease and multiple sclerosis are not associated with autoantibodies against structural proteins of the dermal-epidermal junction. *Br J Dermatol*. 2016; 175:407–409. [PubMed: 26972435]
16. Jour G, Glitza IC, Ellis RM, Torres-Cabala CA, Tetzlaff MT, Li JY, et al. Autoimmune dermatologic toxicities from immune checkpoint blockade with anti-PD-1 antibody therapy: a report on bullous skin eruptions. *J Cutan Pathol*. 2016; 43:688–696. [PubMed: 27086658]
17. Hwang SJ, Carlos G, Chou S, Wakade D, Carlino MS, Fernandez-Penas P. Bullous pemphigoid, an autoantibody-mediated disease, is a novel immune-related adverse event in patients treated with anti-programmed cell death 1 antibodies. *Melanoma Res*. 2016; 26:413–416. [PubMed: 27031539]
18. Carlos G, Anforth R, Chou S, Clements A, Fernandez-Penas P. A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab. *Melanoma Res*. 2015; 25:265–268. [PubMed: 25831416]
19. Naidoo J, Schindler K, Querfeld C, Busam K, Cunningham J, Page DB, et al. Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. *Cancer Immunol Res*. 2016; 4:383–389. [PubMed: 26928461]

Fig. 1.
Biopsy of a pigmented vulvar lesion showing a spitzoid melanoma with a depth of 0.75 mm and numerous mitoses.

Table 1

Reported cases of bullous pemphigoid developing in close association with melanoma without the use of melanoma immunotherapy

Marks [1]	61-year-old woman	Four-month history of oral blistering with new-onset development of cutaneous blisters. At the 1-month follow-up, the patient noted a nevus that had been bleeding intermittently over the course of a year. Following excision of melanoma, the patient's skin lesions, but not oral lesions, resolved without treatment. A significant flare of bullous pemphigoid occurred several months later and she was noted to have an enlarged lymph node containing melanoma. Following removal of the involved node, the patient was able to be controlled on 2.5–5 mg of prednisone per day compared with the 60 mg required before lymph node resection
Parsons and Savin [2]	57-year-old woman	Five months following the diagnosis of bullous pemphigoid, the patient had a melanoma excised from her back. Four years later, the patient had an acute flare of bullous pemphigoid and was noted to have newly discovered metastatic deposits on chest radiograph as well as lymph node invasion
Parimi <i>et al.</i> [3]	74-year-old man	The patient presented with a new-onset severe bullous pemphigoid, requiring hospitalization. One month following hospitalization, the patient was noted to have darkening of the right toe nail bed. Biopsy indicated melanoma, with a chest radiograph showing lung metastases and lymphadenopathy
Beck <i>et al.</i> [4]	72-year-old man	The patient with a previous history of melanoma was found to have recurrent subungual melanoma with positive sentinel nodes. Within 1 year of this recurrence, the patient developed bullous pemphigoid, followed by discovery of distant metastases. Exacerbated with ipilimumab and pembrolizumab treatment
This case	88-year-old woman	An 88-year-old woman initially presented for evaluation of a pruritic rash. At this time, the patient noted a 4-month history of a growing pigmented vulvar lesion, found to be melanoma. Following excision of the melanoma, the patient was able to be managed on doxycycline and niacinamide without flares