A case of nivolumab-induced bullous pemphigoid successfully treated with dupilumab

Manfredo Bruni, Agata Moar, Donatella Schena, Giampiero Girolomoni

Affiliations: Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy

Corresponding Author: Manfredo Bruni, Section of Dermatology and Venereology, Department of Medicine, University of Verona, Piazzale A. Stefani 1, 37126 Verona, Italy, Fax: 39-0458027315, E-mail: manfredo.bruni@gmail.com

Abstract

A 76-year-old man came to our attention for the presence of itchy skin lesions localized on the trunk. The patient had a nodular melanoma removed two years earlier. Because of metastatic pulmonary melanoma, he underwent a lung lobectomy and began adjuvant therapy with nivolumab. After six months of treatment, the patient reported the appearance of itchy lesions on the trunk that were diagnosed as eczema and successfully treated with systemic corticosteroids. Upon corticosteroid discontinuation, the eruption relapsed presenting with erythematous macules, tense blisters, and erosions on the trunk and limbs. The presence of linear deposits of IgG and C3 at the dermo-epidermal junction and high serum levels of anti-BP180 antibodies confirmed the suspicion of nivolumab-induced bullous pemphigoid. Treatment with 0.6mg/kg methylprednisolone and 200mg/day doxycycline as well as nivolumab discontinuation induced temporary remission. After tapering methylprednisolone to 16mg/day, the patient developed new blisters. Therefore, dupilumab 300mg every other week was added with progressive improvement while methylprednisolone was tapered down and withdrawn after four months. After six months the patient was still in full clinical remission. Many cases of conventional bullous pemphigoid have been treated successfully with dupilumab, which can also be used safely in cancer patients without inducing overt immunosuppression.

Keywords: bullous pemphigoid, dupilumab, nivolumab

Introduction

Bullous pemphigoid (BP) is an autoimmune bullous disease characterized by the production of autoantibodies against the hemidesmosomal proteins of the dermo-epidermal junction BP180 and BP230. The gold standard for the diagnosis of BP is the histological evaluation of active lesions and direct immunofluorescence of perilesional skin [1-3]. The former shows the presence of a subepidermal blister with an eosinophilic infiltrate, whereas the latter reveals the presence of a linear deposit of IgG autoantibodies and/or C3 along the dermo-epidermal junction. Serum autoantibodies can be measured in the serum by indirect immunofluorescence or ELISA. Assessment of the serum autoantibody titer trend during follow-up helps in the evaluation of the disease activity in some cases [1,4,5]. Several different drugs such as antihypertensives, antibiotics, NSAIDs, dipeptidyl peptidase-4 inhibitors (e.g., vildagliptin), biological therapies (TNFalpha inhibitors), immune checkpoint inhibitors targeting programmed death-1 (PD1)/ programmed death ligand-1 (PDL1), (pembrolizumab or nivolumab), or anti-cytotoxic T lymphocyte-associated protein-4 (CTLA 4) may induce BP [6-8]. The diagnosis of drug-induced BP is similar to that of idiopathic BP [9]. To discern the two entities, it is important to carry out a detailed personal and pharmacological medical history. To date, there are no studies comparing the frequency of antibodies against BP180 and BP230 between patients with PD1 inhibitors-induced BP and idiopathic BP. Malignant melanocytic tumors are known to express BP180 and it has been assumed

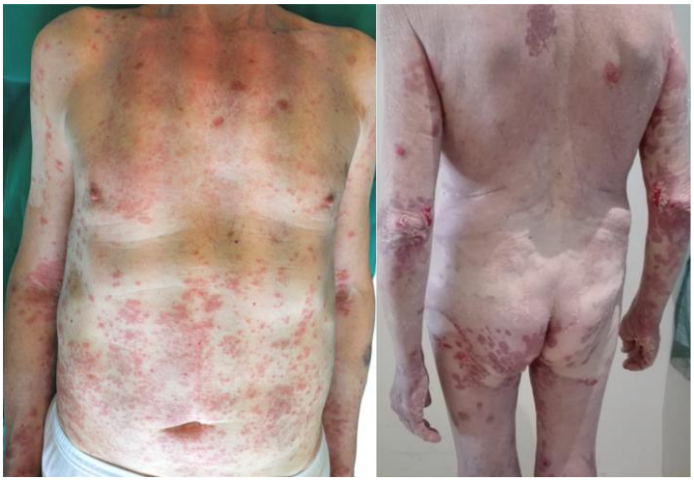

Figure 1. *Eczematous and bullous lesions localized on the trunk and lower limbs.*

that immunotherapy, by stimulating the immune system, may favor the development of antibodies against BP180 that in turn may induce the onset of BP [10]. Therefore, the frequency of antibodies against BP180 in patients with PD1 inhibitor-induced BP could be higher than that of antibodies against BP230.

Case Synopsis

A 76-year-old man came to our attention for the presence of itchy eczematous and bullous lesions localized on the trunk and lower limbs (**Figure 1**). The patient had removed a scalp nodular melanoma (Breslow 9mm, ulcerated, 12/mm^2 mitosis with negative sentinel lymph node) two years earlier. Owing to the appearance of metastatic pulmonary melanoma, the patient underwent a left lung lobectomy and subsequently began adjuvant therapy with nivolumab (480mg every four weeks). After 6 months of treatment there were no signs of melanoma recurrence. For this reason, the patient refused to continue nivolumab therapy as planned. Moreover, he also reported the appearance of itchy lesions on the trunk diagnosed first as eczema and successfully treated with systemic corticosteroids and antihistamines. Upon discontinuation of corticosteroid therapy, the patient had a rapid relapse of the cutaneous eruption and presented with erythematous macules, tense blisters, and erosions throughout the trunk and limbs. Histological examination of the skin showed the presence of a subepidermal bulla rich in eosinophils, while direct immunofluorescence revealed the presence of intense linear IgG and C3 deposits at the dermo-epidermal junction (**Figure 2**). Blood tests revealed increased numbers of eosinophils (0.96×10^9/L) and neutrophils (13.33×10^9/L) and high levels of anti-BP180 (87.37U/ml; n.v. <14 U/ml) without anti-BP230 autoantibodies. Treatment was initiated with doxycycline 100mg twice a day, methylprednisolone 40mg/day IM (0.6mg/kg) for 10 days, and topical corticosteroids. After 10 days of therapy there were no new blisters; topical corticosteroid therapy was discontinued and the systemic corticosteroids were tapered down to limit side effects. However, upon tapering

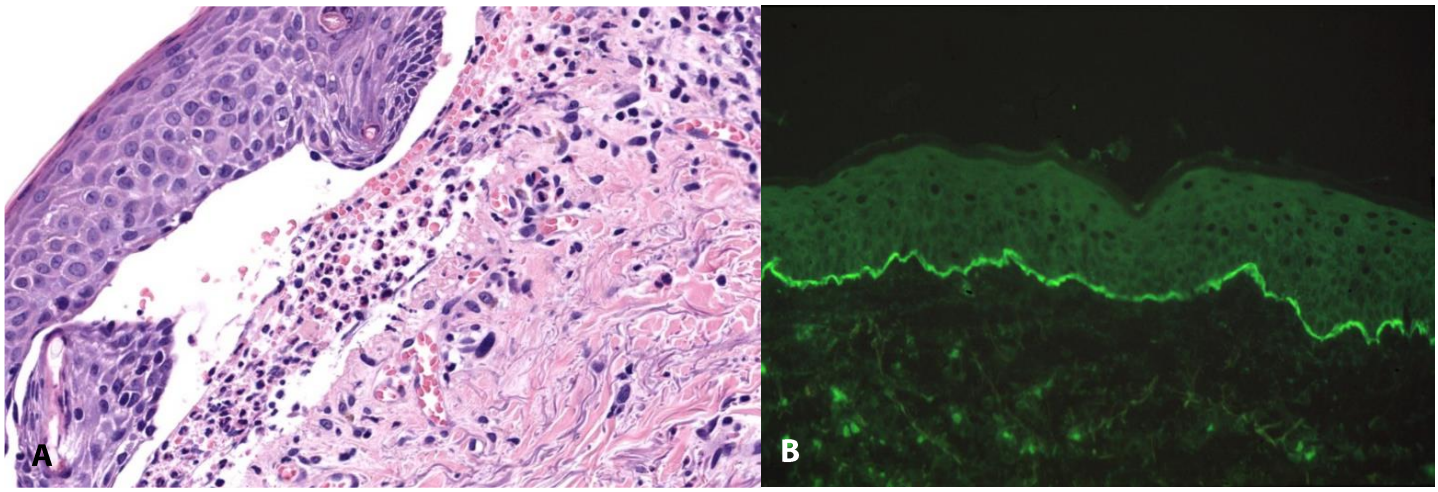

Figure 2. ***A)*** *Subepidermal bullous lesion rich in eosinophils. H&E, 40×.* ***B)*** *Direct immunofluorescence showing intense linear IgG and C3 deposits at the dermo-epidermal junction, 40×.*

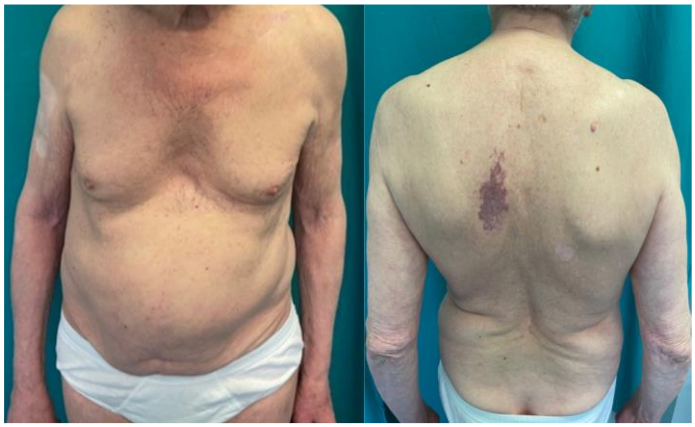

Figure 3. *Clinical remission at 6 months of dupilumab therapy.*

methylprednisolone to 16mg/day, the patient developed new blisters on the trunk, buttocks, and lower limbs. Mycophenolate mofetil, azathioprine, or methotrexate were contraindicated in this patient. Furthermore, the COVID-19 pandemic had just begun and treatment with rituximab was deemed unsafe. Therefore, doxycycline was discontinued, methylprednisolone was increased to 20mg/day, and dupilumab was started at 300mg every other week. After two months, a considerable clinical improvement was observed and methylprednisolone was tapered. After two additional months the patient had no new blisters and only minimal erythema on the buttocks and corticosteroids were stopped; dupilumab only was continued. Six months after dupilumab initiation, the patient was in full clinical remission and is currently continuing monotherapy with dupilumab (**Figure 3**).

Case Discussion

No relevant clinical or immunopathological differences between idiopathic BP and drug-induced BP have been described [7]. Since BP is an immune-mediated disease, it seems plausible that the inhibition of the PD1/PDL1 and CTLA-4 mediated by the immunostimulatory treatments for advanced and metastatic neoplasms may trigger BP [8,11,12]. Indeed, Lopez et al. have described 10 cases of BP induced by pembrolizumab and 9 cases of BP induced by nivolumab [11]. A time lapse of 4-84 weeks between the initiation of pembrolizumab therapy and the development of BP and a time lapse of 3-52 weeks between the onset of nivolumab therapy and the development of BP have been reported [11]. In our case, the patient developed skin lesions 26 weeks after starting nivolumab. Therefore, there is a wide range of time lapse for the development of drug-induced BP, making sometimes this correlation difficult. Patients with drug-induced BP generally respond to topical corticosteroids, tetracyclines, or systemic corticosteroids, whereas immunosuppressive drugs have been used in the most refractory cases or as corticosteroid-sparing agents. In severe drug-induced BP refractory to classic immunosuppressive drugs and rituximab, high-dose intravenous immunoglobulin, omalizumab, and dupilumab have been used with clinical benefit [13,14].

Conclusion

We present a case of nivolumab-induced BP unresponsive to conventional treatment and culprit drug withdrawal, successfully treated with dupilumab. The diagnosis of drug-induced BP may not be straightforward as there could be a large delay between drug initiation and the development of BP. Evaluation of a patient's age and drug regimen could help in making the correct diagnosis. Dupilumab is currently approved for the treatment of atopic dermatitis, asthma, and severe chronic rhinosinusitis with nasal polyps. Evidence is accumulating that it is also effective in other diseases such as chronic urticaria, prurigo nodularis, and BP. Current trials of dupilumab for BP are underway.

Potential conflicts of interest

The authors declare no conflicts of interest

References

1. Moar A, Azzolini A, Tessari G, Schena D, Girolomoni G. Non-bullous pemphigoid: a single-center retrospective study. *Dermatology*. 2021;237:1039-1045. [PMID: 33979792].
2. Cozzani E, Marzano AV, Caproni M, Feliciani C, Calzavara-Pinton P. Cutaneous Immunology group of SIDeMaST. Bullous pemphigoid: Italian guidelines adapted from the EDF/EADV guidelines. *G Ital*

Dermatol Venereol. 2018;153:305-315. [PMID: 29600832].
3. Nishie W. Update on the pathogenesis of bullous pemphigoid: an autoantibody-mediated blistering disease targeting collagen XVII. *J Dermatol Sci.* 2014;73:179-86. [PMID: 24434029].
4. Miyamoto D, Santi CG, Aoki V, Maruta CW. Bullous pemphigoid. *An Bras Dermatol.* 2019;94:133-146. [PMID: 31090818].
5. Messingham KN, Miller AD, Narayanan NS, Connell SJ, Fairley JA. Demographics and autoantibody profiles of pemphigoid patients with underlying neurologic diseases.
6. *J Invest Dermatol.* 2019;139:1860-1866.e1. [PMID: 30876802].
7. Bellinato F, Maurelli M, Schena D, Gisondi P, Girolomoni G. Clinical and immunological profile of patients with dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid. *Ital J Dermatol Venerol.* 2021;156:455-459. [PMID: 32545941].
8. Stavropoulos PG, Soura E, Antoniou C. Drug-induced pemphigoid: a review of the literature. *J Eur Acad Dermatol Venereol.* 2014;28:1133-40. [PMID: 24404939].
9. Siegel J, Totonchy M, Damsky W, et al. Bullous disorders associated with anti-PD1 and anti-PDL1 therapy: A retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy. *J Am Acad Dermatol.* 2018;79:1081-1088. [PMID: 30025829].
10. Sun CW, Grossman SK, Aphale A, Hsu S. Pembrolizumab-induced bullous pemphigoid. *JAAD Case Rep.* 2019;5:362-364. [PMID: 31008169].
11. Tsiogka A, Bauer JW, Patsatsi A. Bullous pemphigoid associated with anti-programmed cell death protein one and anti-programmed cell death ligand one therapy: A review of the literature. *Acta Derm Venereol.* 2021;101: adv00377. [PMID: 33426566].
12. Lopez AT, Khanna T, Antonov N, Audrey-Bayan C, Geskin L. A review of bullous pemphigoid associated with PD1 and PDL1 inhibitors. *Int J Dermatol.* 2018;57:664-669. [PMID: 29630716].
13. Klepper EM, Robinson HN. Dupilumab for the treatment of nivolumab-induced bullous pemphigoid: a case report and review of the literature. *Dermatol Online J.* 2021;27. [PMID: 34755978].
14. Patel PM, Jones VA, Murray TN, Amber KT. A review comparing international guidelines for the management of bullous pemphigoid, pemphigoid gestationis, mucous membrane pemphigoid, and epidermolysis bullosa acquisita. *Am J Clin Dermatol.* 2020;21:557-565. [PMID: 32180161].
15. Abdat R, Waldman RA, de Bedout V, et al. Dupilumab as a novel therapy for bullous pemphigoid: A multicenter case series. *J Am Acad Dermatol.* 2020;83:46-52. [PMID: 32179082].