Letter to the Editor

Bullous pemphigoid associated with pleural mesothelioma: a controversial etiology. Were the bullous lesions induced by pembrolizumab or related to malignancy?

A. Tammaro[1], G.A.R. Adebanjo[1], C. Chello[2], A. Capalbo[1], S. Alexander[1], G. Trischitta[3], M. Pezza[3], E. Cavalieri[4] and P. Pellegrini[5]

[1]NESMOS, Dermatology Department, Sapienza University of Rome, Rome, Italy; [2]Plastic and Reconstructive Surgery Department, Dermatology Section, Campus Bio-Medico, University of Rome, Rome, Italy; [3]Dermatology Department, ASL Benevento, Benevento, Italy; [4]Hematology Department, S. Andrea Hospital, Rome, Italy; [5]Oncology Department, S. Andrea Hospital, Sapienza University of Rome, Rome, Italy

Corresponding author:

Antonella Tammaro

NESMOS Dermatology Department

Sapienza University of Rome

Via di Grottarossa 1035/1039

00189, Rome, Italy

e-mail: tammaroantonella@gmail.com

Tel.: +39 0633775907

***keywords**: bullous pemphigoid, pleural mesothelioma*

To the Editor,

Malignant pleural mesothelioma is an aggressive and histologically heterogeneous tumor with a five-year survival rate lower than 10% (1).

The standard first-line treatment consists of cisplatin and pemetrexed (1). Nevertheless, its combination with anti-programmed cell death protein 1 (PD-1) immunotherapy has shown promising results (1).

We report the case of a 72-year-old white man with advanced pleural mesothelioma and dysphagia who presented to our clinic because of pruritic disfiguring lesions on his skin. The patient's chemotherapy regimen consisted of cisplatin, pemetrexed, and pembrolizumab.

The patient presented multiple erythematous bullous and crusted lesions all over his body (Figure 1), which had appeared after the fourth cycle of chemotherapy. Thence, a biopsy of a specimen including perilesional tissue and skin of the base of one bulla was made: chronic inflammation, lymphocytic infiltration and plasma cells with sparse eosinophils were identified along the basement membrane. In addition, direct immunofluorescence of a frozen specimen showed linear granular deposits of IgG and C3 on the dermo-epidermal junction.

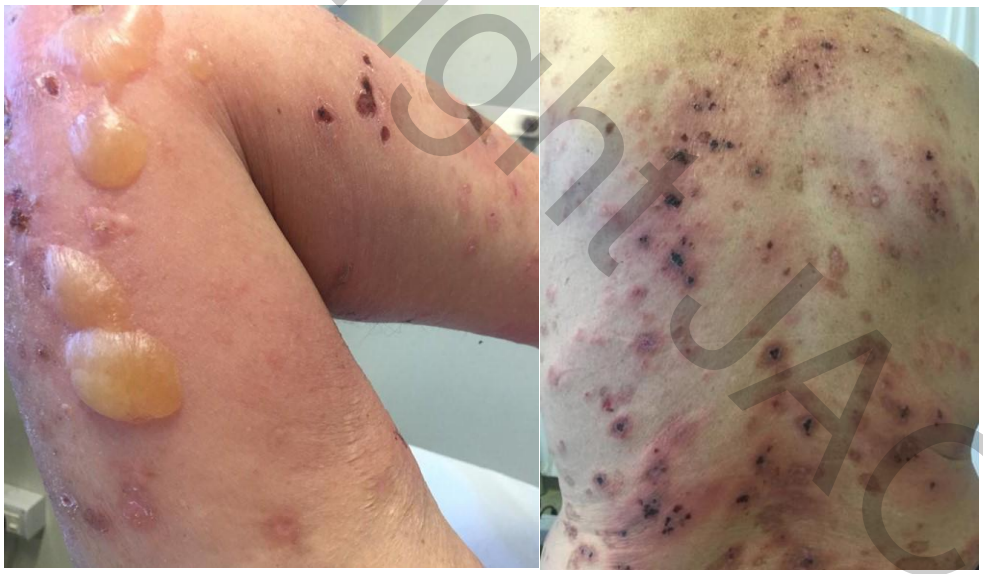

Fig. 1. *Bullous pemphigoid in a patient with malignant pleural mesothelioma. (a) Crusted erythematous lesions on the back of the patient. (b) Yellow/tan colored bullous lesions on the right arm of the patient. Crusted lesions are present as well.*

Given the patient's clinical picture, a bullous pemphigoid diagnosis was made. Therefore, chemotherapy was discontinued, and the patient was given 40 mg of prednisone twice daily. After 10 days, the dose changed to 40 mg of prednisone in the morning and 20 mg in the evening for an additional 7 days, improving the skin lesions.

Notwithstanding, the glucocorticoid therapy combined with chemotherapy interruption failed to tackle the bullous manifestations, whose

appearance started worsening again. A month after the anti-cancer drug administration was halted and prednisone started, the patient was admitted to the hospital because it was clear that the bullous lesions had become refractory to steroid treatment. Indeed, they were extremely painful and pruritic, dramatically impairing his quality of life.

Two weeks later, the patient's condition suddenly deteriorated, resulting in death. Bullous pemphigoid (BP) is an autoimmune disorder characterized by blistering lesions (2), and its etiology is controversial.

Nowadays, the literature has highlighted how BP may be infrequently found in association with the use of anti-PD1 immunotherapy (3). However, drug-induced pathogenesis was not fully supported in our patient, since the interruption of pembrolizumab did not improve dermatosis (3).

Conversely, pemphigoid associated with malignancy (PAM) (a term preferable to paraneoplastic pemphigoid (2) could not be confirmed because of the death of the patient. Furthermore, an autopsy was not performed because the relatives refused to do it.

Moreover, PAM has no clear-cut definition, and its diagnosis criteria are not fully applicable to advanced malignancies (2). As a matter of fact, PAM has been described in the literature. However, due to its rarity, its serological aspects have not been investigated enough and are not well-defined, as is the case of paraneoplastic pemphigus (2).

PAM has recently been associated with squamous cell lung cancer and non-Hodgkin lymphoma (4,5). However, to the best of our knowledge, no reports are linking PAM to mesothelioma.

Numerous hypotheses regarding the occurrence of both PAM and drug-induced pemphigoid have been suggested: hormone-mediated mechanisms, antibody cross-reactivity, genetic polymorphisms, external tumorigenic agents, and tumor-secreted immunoglobulins may be responsible for the appearance of subepidermal blisters (2).

Nevertheless, their pathogeneses is still a matter of debate. Indeed, although the disease did not respond to the suspension of chemotherapy, it does not exclude that the drugs may have acted as triggers to the disease or that tumor-specific factors may have played a role, or both.

It is reasonable to exclude vaccination as a plausible trigger for BP in this patient since no vaccine had been inoculated in temporal proximity to the appearance of the bullous lesions (6). Additionally, the patient did not have any bacterial cutaneous superinfection, which possibly could have provoked the appearance of BP (7,8).

The patient's premature death halted the diagnostic investigations; however, despite the numerous pathogenetic processes that could explain the appearance of BP, the drug-induced and malignancy-associated ones are the most likely.

We may even speculate that both processes may have occurred simultaneously in our patient. The adequate treatment of drug-induced pemphigoid and PAM has yet to be determined, and further studies are needed to elucidate these entities.

Acknowledgments.

Conflict of interest: None.

Funding: none.

References

1. Viscardi G, Di Liello R, Morgillo F. How I treat malignant pleural mesothelioma. ESMO Open 2020; 4(Suppl 2):e000669.
2. Balestri R, Magnano M, La Placa M, Patrizi A, Angileri L, Tengattini V, Bardazzi F. Malignancies in bullous pemphigoid: A controversial association. J Dermatol 2016; 43(2):125-33.
3. Lopez AT, Khanna T, Antonov N, Audrey-Bayan C, Geskin L. A review of bullous pemphigoid associated with PD-1 and PD-L1 inhibitors. Int J Dermatol 2018; 57(6):664-9.
4. Das A, Das S, Das SK, Basuthakur S. A case of paraneoplastic bullous pemphigoid in association with squamous cell carcinoma of lung. J Postgrad Med 2015; 61(3):197-9.
5. Iranzo P, López I, Robles MT, Mascaró JM, Campo E, Herrero C. Bullous pemphigoid associated with mantle cell lymphoma. Arch Dermatol 2004; 140(12):1496-9.
6. Young J, Mercieca L, Ceci M, Pisani D, Betts A, Boffa MJ. A case of bullous pemphigoid after the SARS-CoV-2 mRNA vaccine. J Eur Acad Dermatol Venereol JEADV 2022; 36(1):e13-6.
7. Biondo MI, Fiorentino C, Persechino S, et al. May Bacterial Infections Trigger Bullous Pemphigoid? Case Report and Review of Literature. Microorganisms 2021; 9(6):1235.
8. Löffel FB, Stücker M. Localized bullous pemphigoid triggered by erysipelas. Hautarzt Z Dermatol Venerol Verwandte Geb 2016; 67(10):829-32.