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CASE REPORT

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Refractory bullous pemphigoid during treatment with pembrolizumab in the first-line treatment of advanced non-small cell lung cancer

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ABSTRACT

Dermatological toxicity is one of the most common immune-related adverse events (irAEs) of treatment with immune checkpoint inhibitors (ICIs). Bullous pemphigoid (BP) is a rare and serious complication of these drugs that can be difficult to establish, as its initial symptoms may be indistinguishable from mild skin lesions. This paper presents the case of a 68-year-old patient who developed BP after receiving one of the ICI therapies, pembrolizumab, for advanced non-small cell lung cancer (NSCLC). After approximately 7 months of therapy, a grade 3 skin toxicity in the Common Terminology Criteria for Adverse Events (CTCAE) occurred in the form of rash and pruritus. Pembrolizumab was then held and prednisone and antihistamines were introduced. When dermal toxicity improved to grade 1, pembrolizumab was resumed and prednisone was kept at a dose of 10 mg. Immunotherapy was discontinued 3 months later, after the recurrence of grade 3 skin toxicity symptoms. When the patient developed blisters filled with clear fluid, dermatologists suspected pembrolizumab-induced bullous pemphigoid. Bullous pemphigoid was subsequently confirmed using a direct immunofluorescence test and histopathological examination. The patient's skin condition improved after the use of steroid therapy and methotrexate, and the cancer process stabilized for over one year. Cancer progression and deterioration of the patient's general condition were observed approximately 4 months after the termination of pembrolizumab therapy. The paper also discusses the key aspects of ICIs-induced BP, especially pembrolizumabinduced BP in the first-line treatment of metastatic NSCLC. Early diagnosis of skin lesions and the initiation of appropriate treatment may lead to better outcomes for patients and prevent disruptions in immunotherapy.

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Keywords: bullous pemphigoid, pembrolizumab, immune adverse events, immune checkpoint inhibitors, immunotherapy

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized the oncological treatment of many solid tumours. One of the ICIs is pembrolizumab, a humanized anti-programmed cell death-1 (PD-1) monoclonal antibody. Pembrolizumab is currently registered for many indications. Its effectiveness as a monotherapy has been demonstrated in the first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose percentage of tumour cells expressing programmed death-ligand 1 (PD-L1) tumour proportion score is at least 50% (KEYNOTE-024 study) [1]. On the other hand, ICIs non-specifically activate the immune system, thereby inducing immune-related adverse events (irAEs), including severe ones [2]. Cutaneous toxicity is one of the most common irAEs, occurring in 30–40% [3] of patients treated with ICIs (according to other sources, 30–50% of patients [4]). The most common dermal irAEs include pruritus, rashes, vitiligo, and lichenoid reactions [3, 4]. The development of bullous pemphigoid (BP) has been reported in approximately 1% [4] or 0.6% [2] of patients treated with anti-PD-1/PD-L1 antibodies. In the following section of the paper, a case of a patient with pembrolizumab-induced BP during first-line treatment of advanced NSCLC is described.

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CASE REPORT

The patient, a 68-year-old male ex-smoker with metastatic squamous cell carcinoma of the right lung with PD-L1 70%, was admitted for treatment to the oncology department in August 2021. The patient was qualified for immunotherapy with pembrolizumab. In the first computed tomography assessment in October 2021, the disease was stable according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) criteria. It was also the best possible response to treatment obtained during immunotherapy.

In April 2022, the patient reported the appearance of a rash and itching. Physical examination of the trunk and upper limbs skin revealed flat-convex papular lesions with an erythematous base and excoriations. Because of a suspicion of a grade 3 dermal irAE [according to the Common Terminology Criteria for Adverse Events (CTCAE)], pembrolizumab was discontinued, and prednisone at a dose of 0.5 mg/kg and antihistamines were introduced following the European Society for Medical Oncology (ESMO) guidelines.

At the end of April 2022, dermal toxicity decreased to CTCAE grade 1. Pembrolizumab was resumed and prednisone was kept at a dose of 10 mg. In June 2022, the patient reported severe pruritus and rash. Immunotherapy was permanently discontinued due to recurrent skin toxicity in CTCAE grade 3. According to the dermatologist's recommendations, the patient took prednisone at a dose of 20 mg, antihistamines, and an anti-inflammatory ointment.

Over 10 months, the patient received a total of eleven pembrolizumab infusions: nine cycles of 200 mg every 3 weeks and two cycles of 400 mg every 6 weeks. The last cycle of pembrolizumab was administered in May 2022 at a dose of 200 mg. At the end of July 2022, blisters developed on the patient's trunk and limbs. Blisters, filled with transparent fluid, left painful erosions after rupture (Fig. 1).

Bullous pemphigoid was diagnosed histopathologically in August 2022. A direct immunofluorescence examination (DIF) confirmed the diagnosis. Positive pemphigoid antibodies were detected at a titre of 1:80 in the IgG class. Pembrolizumab-induced pemphigoid was suspected. At the turn of August and September 2022, due to the significant severity of skin lesions, the patient was hospitalized in the dermatology department. The treatment included an intravenous steroid, hydrocortisone (3 mg/kg/day), and subcutaneous methotrexate at a dose of 15 mg once a week. After the first week of treatment, hydrocortisone was replaced with oral methylprednisolone (0.4 mg/kg/day) and topical clobetasol propionate 0.05% cream twice a day over the entire body, except the face (30––40 g daily). Methylprednisolone and clobetasol propionate 0.05% cream were gradually reduced from an initial dose,

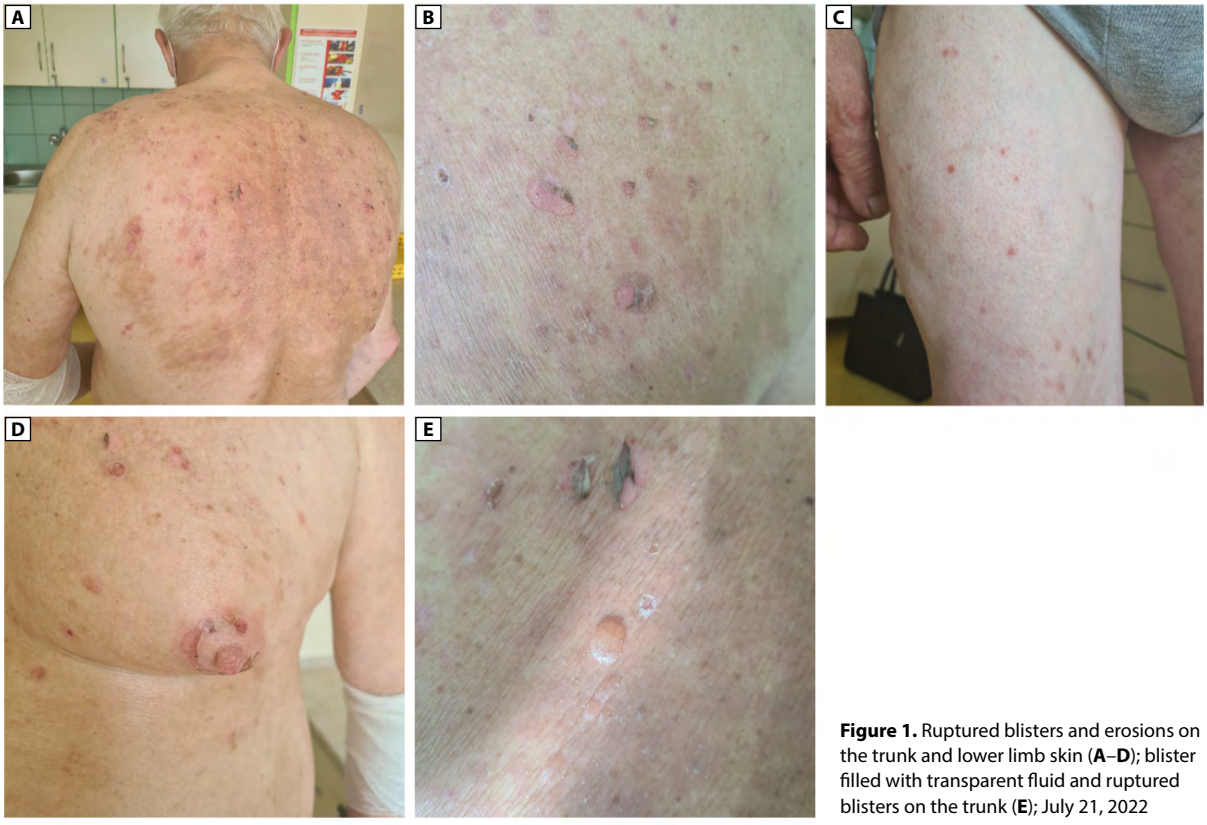

Figure 1. Ruptured blisters and erosions on the trunk and lower limb skin (**A**–**D**); blister filled with transparent fluid and ruptured blisters on the trunk (**E**); July 21, 2022

and methotrexate therapy was continued at a dose of 15 mg subcutaneously every 7 days. The symptoms of pemphigoid disappeared, but within a short period, the patient experienced abdominal pain, weight loss, and hyperglycaemia. Magnetic resonance imaging of the abdomen, performed in September 2022 during hospitalization, revealed the presence of a pathological, ill-defined mass of approximately 85 × 60 × 55 millimetres in retroperitoneal space on the left side. During the diagnosis, which was delayed due to COVID-19, the progression of cancer was confirmed. Due to the deterioration of the patient's general condition, further oncological treatment was discontinued.

DISCUSSION

Accounting for 80% of cases, bullous pemphigoid is the most common autoimmune subepidermal bullous disease with autoantibodies directed against the antigens BP180 (BPAG2 or type XVII collagen) and BP230 (BPAG1). Antigens BP180 and BP230 are parts of hemidesmosomes, responsible for adhesion between epidermal keratinocytes and the basement membrane zone. BP most commonly occurs in patients between the ages of 60 and 80. Because BP mainly affects the elderly population, the mortality rate is increased and ranges from approximately 10 to 40% [5].

Bullous pemphigoid may be induced by drugs such as diuretics, gliptins, beta-blockers, and PD-1/PD-L1 inhibitors [5]. The overall incidence rate is 4.19 per 100,000 person-year [2]. The symptoms of drug-induced BP are similar to idiopathic ones. They appear within 3 months after starting treatment and are usually observed in younger patients. In the prodromal phase of pemphigoid, the symptoms are often non-specific and include itching occurring without skin lesions or with papular or urticarial lesions. Within a few weeks or months, blisters appear over normal skin or an erythematous background. They are most often located on the flexural surfaces of the limbs and the lower part of the trunk [5, 6]. Lesions in the oral cavity occur in approximately 10–30% of patients. [6] The blisters have a tight lid and contain clear fluid, sometimes tinged with blood. After rupturing, they leave erosions and scabs. Eosinophilia may be present in blood laboratory tests [5–7].

Most cases of pemphigoid caused by anti-PD-1/PD-L1 described in the literature concern mainly male patients with an average age of approximately 72 years, diagnosed with melanoma, followed by NSCLC [2, 8].

Compared to most skin toxicities, which are usually the earliest irAEs to appear during the use of ICIs, pemphigoid develops with a delay, on average after approximately 14 weeks after the initiation of anti-PD-1/PD-L1 therapy [7]. According to other analyses, pruritus appears later, on average between weeks 19–21, while blisters may occur in weeks 20–39 of therapy [6]. According to available reports, in patients treated with pembrolizumab, the median time to dermal toxicity was 4 months, and the median time to bullae formation was 7.35 months [2]. Unlike traditional drug-induced BP, ICIs-related BP may persist for several months after discontinuation of immunotherapy due to persistent immune system activation [7] and, as a result, can be difficult to diagnose. To diagnose BP, it is necessary to confirm the presence of typical skin lesions and the result of a direct immunofluorescence examination, which shows linear deposits of IgG and/or C3 at the dermal-epidermal junction. In individual cases of BP, linear IgE deposits occur along the basement membrane zone as the only immunological component or in addition to IgG. Histopathological examination is helpful in the diagnosis but cannot be used for its basis. To determine the characteristics of the antigen or antigens recognized by autoantibodies, enzyme-linked immunosorbent assay (ELISA) tests are performed. ELISA results correlate with the extent of skin lesions and disease activity and can be a tool for monitoring treatment and predicting the recurrence of skin lesions. Additionally, an indirect immunofluorescence (IIF) test can be performed, where BP is characterized by a linear basement membrane zone staining pattern with IgG [9].

The pathogenesis of BP during ICI treatment is still unclear; it is possible that ICIs cause de novo induction of BP or unmask subclinical disease [4]. The mechanism of pemphigoid formation induced by anti-PD-1 and PD-L1 antibodies is probably related to a reduction in the number of regulatory T cells, which leads to increased T cell activation, B cell proliferation, and autoantibody synthesis [6]. Moreover, BP 180 is an antigen that also occurs in cancer cells, melanoma, and NSCLC. Some studies suggest that BP occurs as a result of the binding of overactive T lymphocytes to the BP180 antigen on both cancer cells and the basement membrane of the skin [4, 8].

ESMO guidelines for dermal irAEs recommend using topical and systemic steroid treatments and depending on the severity of BP and the response to medication, temporary or permanent discontinuation of ICI therapy [10]. Alternative treatment modalities include, among others, tetracyclines, niacinamide, methotrexate, dapsone, azathioprine, mycophenolate mofetil, plasma exchange, intravenous immunoglobulin, rituximab, infliximab, omalizumab, and dupilumab [2, 8, 9, 11, 12]. Most patients treated with PD-1/PD-L1 inhibitors who developed BP had to discontinue immunotherapy [2, 3, 8]. In reported cases, patients were treated with local therapy, and most of them required additional systemic treatment with corticosteroids. However, routine glucocorticoid application may lessen the effectiveness of immunotherapy [2, 8]. Certain

dermal irAEs (namely lichenoid and vitiligo) occurring during anti-PD-1/PD-L1 therapy were associated with better response and overall survival [8, 13, 14]. Some retrospective data link the development of BP with improved response to PD-1 treatment, but others do not support these reports [2, 8]. Further observations are therefore necessary.

Due to the increasing morbidity and significant mortality associated with bullous pemphigoid and its often-non-specific course, it is important to remain vigilant in the event of skin lesions appearing during ICI treatment.

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Writing, conceptualization, data analysis, results discussion, editing and review — RO; visualization, patient's attending physician, review and supervision — MR-G; supervision — SM.

Conflict of interest

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Ethics statement

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