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Pemphigus in a Patient Treated with Immune Checkpoint Inhibitor for Advanced Cutaneous Squamous Cell Carcinoma

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ABSTRACT

Cutaneous squamous cell carcinoma is the second most common skin cancer. Cemiplimab, an antiPD-1 monoclonal antibody, is the first immunotherapy approved for patients with locally advanced cSCC. Phase I and II studies showing high antitumor activity and good tolerability of cemiplimab. However, very little data is available on cemiplimab in real life and in frail, elderly and immunocompromised patients. We report the case of an elderly patient (84 years old) affected by metastatic cSCC. The patient performed 16 cycles of treatment with cemiplimab with complete pathological response. A few days after the administration of the 16th cycle of cemiplimab, the patient experienced a severe skin reaction, G4. Clinical examination of the patient revealed diffuse involvement of the trunk, extremities, and oral mucosa with large blisters on the skin, with serum content, excoriations, and large necrotic hemorrhagic eschar on the face (lips). After about a month of high-dose steroid therapy, the patient showed a progressive improvement of the skin lesions but developed a progressive condition of anemia, thrombocytopenia and leucopenia with a condition of sepsis. After one month of targeted antibiotic therapy the sepsis resolved. Currently, after three months of hospitalization, the patient is well and has returned home.

Key word: squamous cell carcinoma, immune checkpoint inhibitor, pemphigus, sepsis

Abbreviations:
cSCC: Cutaneous squamous cell carcinoma;
PD1: programmed death 1;
ICi: immune checkpoint inhibitor;
ORR: objective response rate;
CTLA-4: cytotoxic T lymphocyte antigen-4;
PD-L1: PD-1 ligand;
irAEs: immune-related adverse events.

INTRODUCTION

cSCC represents one of the most common cancers with an increasing incidence. Its diagnosis rarely occurs in the metastatic stage and generally has a good prognosis, with 5-year survival of about 98% (1). Systemic therapy is recommended for the primary treatment of patients with disease unfit for both surgery and radiotherapy. The mutation burden of cSCC is high, and the disease risk is increased among patients with immunosuppression. cSCCs are generally hypermutated tumors due to skin damage from ultraviolet light, and patients who have tumors with a high expression of the neoantigen are more likely to have a response to ICi therapy. Cemiplimab is a high-affinity, highly potent human monoclonal antibody directed against PD1. In the phase I study of cemiplimab, a deep and durable response was observed in patients with advanced cutaneous squamous-cell carcinoma. In 2020, a phase II pilot trial had estab-

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lished the clinical benefit of cemiplimab, as measured by an ORR. It was showed antitumor activity and an acceptable safety profile in patients with locally advanced (2). In 2018, FDA approved cemiplimab for patients with metastatic cSCC or locally advanced cSCC who are not candidates for curative surgery or curative radiation. The use of ICIs is related to an increase in adverse skin reactions such as rash, erythema multiforme, pemphigoid. We report the first case of a patient who developed pemphigus vulgaris and subsequent sepsis during cemiplimab therapy for metastatic cSCC.

CASE REPORT

May 2022, an 84-year-old Caucasian man, with a history of type II diabetes, previous myocardial infarction treated with PCI (1990), kidney stones, cholecystectomy, chronic renal failure, gallstones with biliary stent implantation, presented large ulcerated bilateral parotid tumors. In January 2022, the patient had undergone exeresi of a scalp tumor with a diagnosis of squamous cell carcinoma, well differentiated ulcerated infiltrating the subcutaneous adipose connective tissue, margins free from neoplasm. June 2022, he performed a CT scan which showed a right intraparotid lesion of 56x53x34 mm which infiltrates the masseter muscle and the skin which cannot be clearly dissociated from the zygomatic arch and the mandibular branch, also an increase in the associated adenopathies in the right jugular area of 26x25 and 18x8 mm which compress the vein of the same name and imprint the sternocleidomastoid muscle and the submandibular gland bolar; of the two parathyroid tumors to the left, the cranial one is slightly increased by 18x15 mm, infiltrates the skin and continues downwards until it reaches the site of the caudal one which, on the contrary, is no longer clearly identifiable, this evolution suggests malignant adenopathic flow. Appearance of 14x11 mm adenopathy in the left supraclavicular site. In the chest, a 25x27 mm nodule in the anterior segment of the right upper lobe. Left parotid biopsy confirmed the diagnosis of moderately differentiated squamous cell carcinoma with skin primary. From June 2022 to May 2023, he performed 16 treatment cycles with cemiplimab with complete pathological response. A few days after the administration of the 16th cycle of cemiplimab, the patient experienced a severe skin reaction, G4. Clinical examination of the patient revealed diffuse involvement of the trunk (*fig. 1*), extremities and oral mucosal with large blisters on the skin, with serum content, excoriations and large necrotic hemorrhagic eschar on

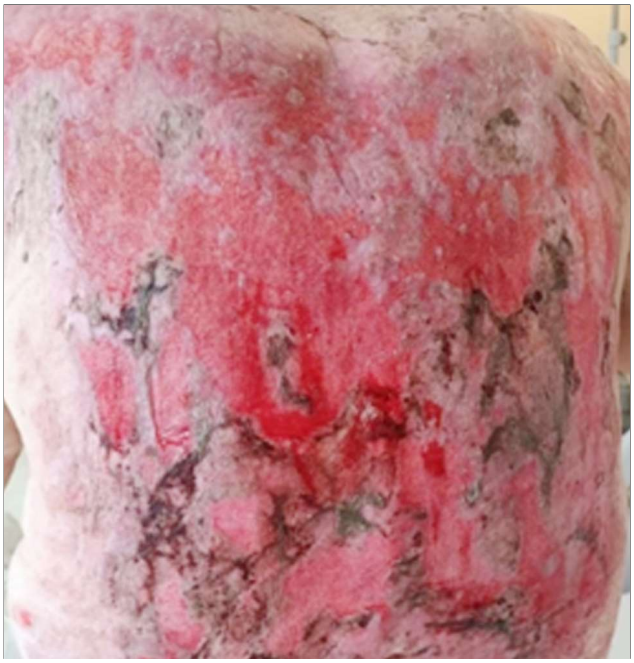

Figure 1 - May 2023, large blisters and excoriations on the trunk of the patient.

the face (lips). Suspecting an adverse reaction to cemiplimab, the patient was administered systemic steroid and antibiotic therapies. The dermatological consultation considering the positivity of serum IgG antibodies against desmoglein gave a diagnosis of pemphigus vulgaris. After about a month of high-dose steroid therapy, the patient showed a progressive improvement of the skin lesions (*fig. 2*) but developed a progressive condition of anemia, thrombocytopenia and leucopenia with a condition of sepsis. One month

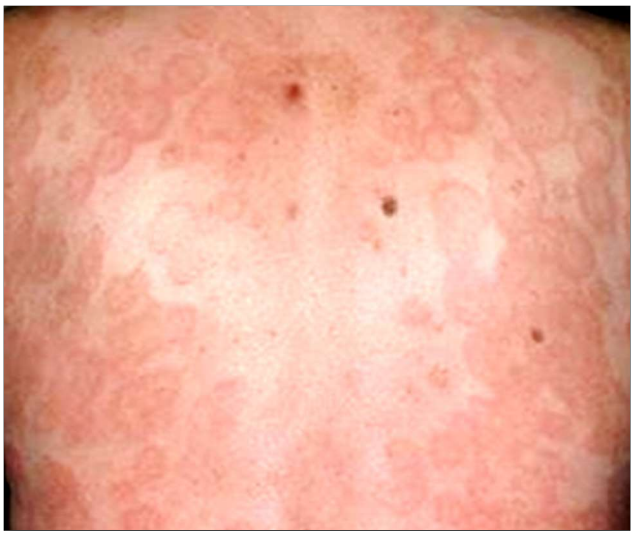

Figure 2 - August 2023, patient's trunk rash after high-dose steroid treatment.

of targeted antibiotic therapy the sepsis resolved. Currently after three months of hospitalization, the patient is well and has returned home, with the indication to repeat a CT scan in 3 months.

DISCUSSION AND CONCLUSION

ICIs are monoclonal antibodies targeting CTLA-4, PD-1, or PD-L1. ICI are approved for the treatment of malign cancer in various disease settings. CTLA-4 is a brake mechanism in immune response. PD-1/PD-L1 pathway controls the induction and maintenance of immune tolerance within the tumor microenvironment. The activity of PD-1 and its ligands PD-L1 is responsible for T cell activation, proliferation, and cytotoxic secretion in cancer. Blocking the local tumor-specific immune response can lead to long-term tumor control. ICIs may be responsible for specific toxicities called irAEs, as a consequence infiltration of normal tissues by activated T lymphocytes that are responsible for autoimmunity (3).

The mechanisms leading to the development of immune-related adverse events are not clear, but they appear to be T-cell mediated. Blockade of the PD-1/PDL-1 pathway, the activity of regulatory T cells is reduced resulting in the activation of B and T lymphocytes in the production of antibodies. 30-40% of patients treated with ICIs show adverse skin reactions. They manifest clinically maculopapular rash, pigmentation changes, eczematous dermatitis, psoriasis, lichenoid dermatitis, vitiligo, pruritus, vesicular disorders (4).

Only one case of pemphigus vulgaris in a patient treated for metastatic cSCC with cemiplimab is described in the literature (5). Some cases of pemphigus vulgaris have occurred during treatment with nivolumab and pembrolizumab. Krammer et al. described a case of pemphigus vulgaris in an 85-year-old Caucasian patient after 9 cycles of treatment with nivolumab, in this case the patient had already developed pemphigus vulgaris about 15 years earlier. After 8 weeks of therapy with prednisone and methotrexate, the patient achieved complete remission of the skin lesions (6). Rohan Garje et al. reported a case of pemphigus vulgaris in a 64-year-old patient after a cycle of treatment with pembrolizumab for bladder cancer. The patient had a history of pemphigus vulgaris in remission (7). In both cases described, the patients had a history of at least one episode of pemphigus vulgaris. In our case, the patient had no history of pemphigus or autoimmune skin disease.

Pemphigus is an autoimmune disease. Auto-antibodies determine the interruption of keratinocyte adhesion, a phenomenon called "acantholysis". Genetic, environmental factors, infections, drugs, hormones, environment, can trigger the formation of auto-antibodies (8). The immune system innates and adaptive are both involved in pathogenesis of pemphigus. Cells of innate immunity are rarely detected in lesional skin, for this reason their role in the pathogenesis of pemphigus is limited. Specifically, NK cells stimulate CD4+ T lymphocytes to secrete proinflammatory cytokines directly involved in the pathogenesis of pemphigus. In the context of adaptive immunity, with activation of Th1/Th17 was observed an elevation of inflammatory cytokines IFN-γ (Th1), IL-17, and IL-23 (Th17) with simultaneous decrease in IL-10 and IL-2. In addition, the number of regulatory T cells in pemphigus patients is reduced which creates an imbalanced immune response (9).

We have described the case of an elderly patient who manifested a G4 vulgaris pemphigus. Very few data are available regarding cemiplimab in real-life experience and in frail, elderly, and immunosuppressed patients. Strippoli et coll., in real-life experience, demonstrated that cemiplimab has high antitumor activity with an acceptable safety profile in frail, elderly, and immunosuppressed patients. 33% of patients in the study experienced skin toxicities such as pruritus and rash, only one patient developed bullous erythema (10).

Our case demonstrated the efficacy of cemiplimab considering the complete response to treatment, but remain open as the possibility of stopping treatment when a response is achieved and the long-term tolerability of treatment.

Authorship

All authors confirm that they have met the criteria for authorship as established by the International Committee of Medical Journal Editors.

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Conflicts of Interest and Source of Funding

The authors have no conflicts of interest to declare.

Ethics approval

The research was conducted ethically in accordance

with the "World Medical Association Declaration of Helsinki". Study approval statement: ethics approval was not required by Department of Oncology of Siracusa ethical commission. Consent to publish statement: written informed consent was obtained from the participant for the publication of the details of his medical case and accompanying image.

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