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CASE REPORT

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Pulmonary Toxicity of Pembrolizumab

Toxicidad pulmonar por pembrolizumab

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ABSTRACT

We present the case of a patient diagnosed with metastatic lung adenocarcinoma who, after five months of treatment with pembrolizumab, presented grade 2 pneumonitis, interpreted as pembrolizumab toxicity, with a good response and resolution of the infiltrates with the suspension of the immunomodulator and the administration of corticosteroids.

Key words: Pembrolizumab; Pulmonary Toxicity; PD-L1 Positive; non-small cell lung cancer (NSCLC)

RESUMEN

Se presenta el caso de un paciente con diagnóstico de adenocarcinoma de pulmón metastásico que, luego de realizar cinco meses de tratamiento con pembrolizumab, presentó neumonitis grado 2, interpretada como toxicidad por pembrolizumab con buena respuesta y resolución de los infiltrados con la suspensión del inmunomodulador y la administración de corticoides.

Palabras clave: Pembrolizumab; toxicidad pulmonar; PD-L1 positivo; cáncer de pulmón de células no pequeñas (CPNCP)

INTRODUCTION

Pembrolizumab is a monoclonal antibody designated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express the programmed death-ligand 1 (PD-L1) surface protein.[1-2] (Fig. 1).

Pembrolizumab extends survival and has a favorable risk-benefit profile in patients with advanced, PD-L1 positive NSCLC. It is considered a new treatment option.[3] Immunomodulators have revolutionized cancer therapy, but it should be noted that early detection and treatment of adverse effects is critical. While they have a relatively mild toxicity profile, immune-mediated adverse effects can occur and be severe.

CASE REPORT

65-year old man with history of smoking, arterial hypertension, chronic obstructive pulmonary disease (COPD) (with a forced expiratory volume in the first second [FEV1] of 78%), heart failure, dyslipidemia, and benign prostatic hyperplasia. He was under the care of the Oncology Service due to a lung adenocarcinoma in the upper right lobe. The surgical biopsy revealed the following mutation pattern: positive for CK7, non-mutated EGFR, negative for ALK, PD-L1 positive with a tumor proportion score (TPS) of

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60%. The chest tomography showed a lung opacity in the upper right lobe with spiculated heterogeneous borders in pleural contact, along with nodules in the middle lobe and lower left lobe (Fig.2).

After five months of treatment with pembrolizumab, he developed dyspnea and cough with a drop in oxygen saturation, so he was referred to the Pulmonology Department. A chest X-ray was performed, revealing bilateral heterogeneous infiltrates (Fig. 3A). The chest tomography showed an image with spiculated borders and cavitation in the upper right lobe, extending to the lower lobe, measuring 76 × 45 mm. Additionally, there were nodules in the middle lobe and lower left lobe with associated interstitial infiltrates. Right hilar and mediastinal lymphadenopathy were observed. A superinfection was ruled out (Fig. 3B).

The case was presented in a multidisciplinary medical conference, and it was agreed to discontinue the treatment with pembrolizumab since the dyspnea and new infiltrates were interpreted as toxicity-related. In addition, the patient started with 40 mg/day of methylprednisolone with clear improvement after 15 days. The condition was interpreted as cryptogenic organizing pneumonia secondary to pembrolizumab. After 5 months of corticosteroid treatment, the patient no longer had respiratory symptoms and showed significant improvement in radiological infiltrates (Fig. 4A and 4B). Treatment with steroids was considered concluded.

During the following months, the patient was awaiting second-line treatment. He received radiotherapy as he developed bone metastases. Subsequently, he had intercurrent SARS-CoV-2 infection, which required hospitalization, and he passed away.

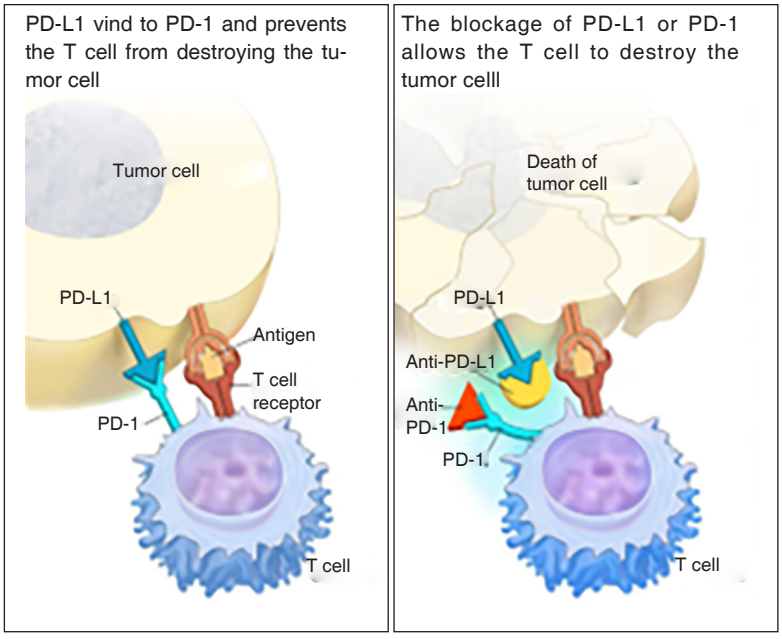

Figure 1. Inhibitors of immune activation checkpoints.

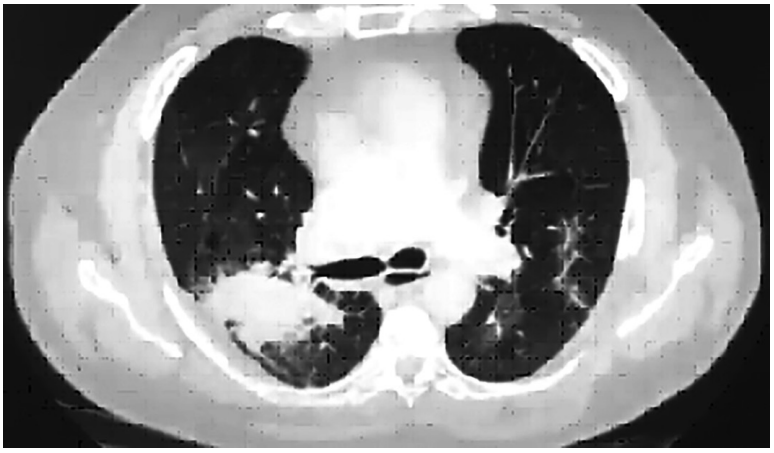

Figure 2. Chest tomography before pembrolizumab.

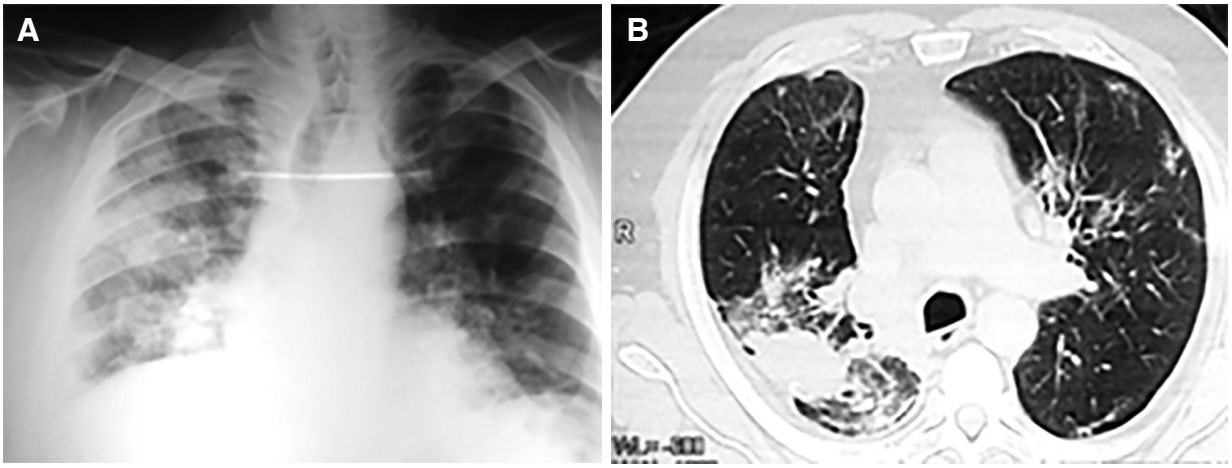

Figure 3 **A.** Chest X-ray on admission. **B.** Chest tomography on admission.

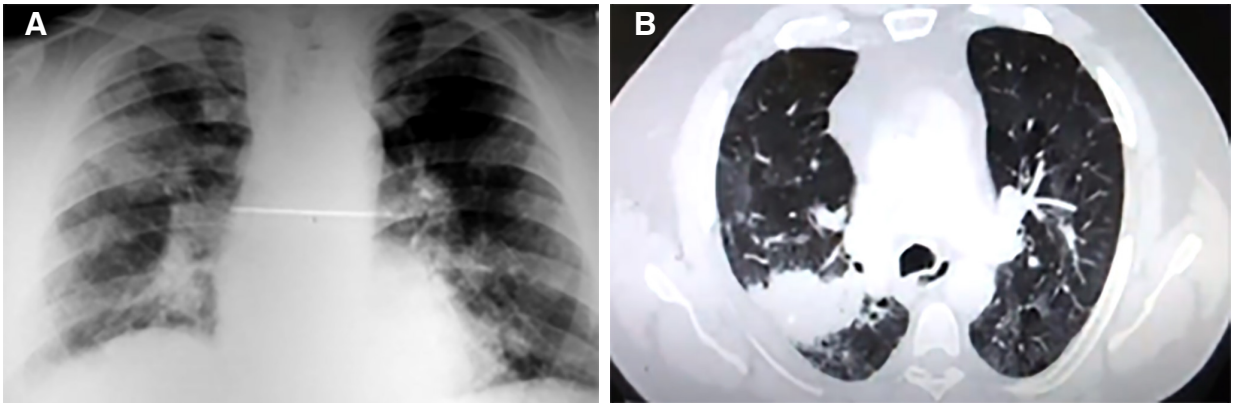

Figure 4. **A.** Chest X-ray 2 months after beginning treatment with corticosteroids. **B.** Chest tomography after the use of corticosteroids.

DISCUSSION

PD-1L is present in tumor cells and has a protective effect on them. Pembrolizumab is a highly selective humanized monoclonal antibody against PD-1, designed to block the interaction between PD-1 and its ligands, thus enhancing anti-tumor cellular activity.[1]

Preclinical studies have shown that radiotherapy also improves anti-tumor immune responses. In an evaluation of 98 patients comparing pembrolizumab treatment with and without radiotherapy, the progression-free survival in the group receiving pembrolizumab and radiotherapy was significantly higher than in patients without prior radiotherapy.[4] The adverse effects of a group of over 500 patients who received pembrolizumab were ranked in order of frequency as follows: fatigue, decreased appetite, dyspnea, and cough. The most common immune-related adverse events were thyroid disorders (hypothyroidism and hyperthyroidism). The most severe adverse events included pleural effusion, pneumonia, dyspnea, pulmonary embolism, and pneumonitis (occurring in 3.5% of patients)[5]. Pneumonitis was more frequently observed in patients with a history of COPD, asthma, or in those who had received localized chest radiotherapy. In a study involving 915 patients treated with anti-PD-1 therapy, 43 developed pneumonitis, and one of those patients died during the immunosuppressive treatment. The onset of symptoms varied widely, ranging from days to over a year. Patients presented with dyspnea and cough as the most frequent symptoms of pneumonitis, while fever and chest pain were reported in a smaller proportion of cases. Some patients did not show any symptoms at the beginning of the pneumonitis, and over 50% showed

other immune-mediated manifestations such as hypophysitis, thyroiditis, or arthritis. The diagnosis of pneumonitis is suspected basing on the presence of new progressive pulmonary infiltrates. Computed tomography is the imaging technique of choice. The most frequent CT findings were cryptogenic organizing pneumonia[6] and ground-glass opacities.[7-8] The management of pneumonitis depends on its clinical and radiological severity.[7]

On the other hand, Fujita et al reported a case of diffuse interstitial lung disease following thoracic surgery in a patient who had previously received pembrolizumab as neoadjuvant treatment. We believe that the case we presented emphasizes the importance of frequently monitoring potential adverse effects associated with the treatment of NSCLC with immunomodulators, given their potential severity and the favorable response that pulmonary toxicity caused by pembrolizumab shows to systemic corticosteroids.[9]

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