Interstitial nephritis secondary to treatment with pembrolizumab, a rare complication in two patients with lung adenocarcinoma

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Abstract

Immune checkpoint inhibitors (ICPi) have become nowadays one of the most widely prescribed anticancer treatments. Pembrolizumab is a highly selective monoclonal immunoglobulin approved as a first-line monotherapy treatment in adult patients with untreated advanced non-small cell lung cancer (NSCLC) with programmed cell death 1 (PD-L1) expression greater than 50% and lack of mutations. ICPi can precipitate immune-related adverse events. Data on the incidence and characteristics of nephrotoxicity from ICPi are limited and caused largely from small case series and oncologic studies. Two patients with a diagnosis of pulmonary adenocarcinoma, undergoing treatment with pembrolizumab who manifested interstitial nephritis secondary to this treatment, are presented below. The growing use of immunotherapy in the treatment of cancer imposes the physician's attention to possible adverse effects.

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Introduction

Ever since its introduction for clinical use, immunotherapy with anti-programmed cell death 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) has revolutionized the treatment of patients with advanced NSCLC [1-3]. The side effects and immune related adverse events associated with PD-1 blockade are generally considered to be well tolerated and manageable. Renal toxicity is a rare complication that deserves medical attention [1,4]. Two patients with a diagnosis of pulmonary adenocarcinoma undergoing treatment with pembrolizumab who manifested interstitial nephritis secondary to this treatment are presented below.

Case Report #1

A 67-year-old woman, who never was a smoker, with no relevant history, was diagnosed with initial stage lung adenocarcinoma IVb (Classification of Malignant Tumours - TNM 8th edition), with bone, contralateral lung and brain metastases, in May 2020. PD-L1 expression was greater than the next generation sequencing (NGS) did not identify target mutations. She started 1st line treatment with pembrolizumab 200mg every 3 weeks in June 2020. At the 8th treatment cycle, the patient had a serum creatinine (sCreat) of 3.5 mg/dl (baseline sCreat 0.7mg/dl), without any associated symptoms. The renal ultrasound excluded obstruction. Urinary sediment showed leukocyturia (>50 leukocytes/field), without erythrocyturia. She was observed by nephrology and after excluding other causes, the diagnosis of interstitial nephritis secondary to pembrolizumab was considered. Treatment with pembrolizumab was suspended and prednisolone 1 mg/kg/day was started and maintained a full dose for 1 month. Then she started tapering prednisolone until a maintenance dose of 10 mg/day, with consequent normalization of renal function (sCreat 1.1 mg/dl). Therapy with pembrolizumab was restarted in February 2021, maintaining treatment with prednisolone 10 mg/day, in slow reduction, for 4 months, with good clinical and analytical tolerance.

Case Report #2

A 67-year-old male, diagnosed with stage IVb pulmonary adenocarcinoma, PD-L1 positive (1-5%), NGS without target mutations. He underwent 1st line treatment with 4 cycles of carboplatin/pemetrexed and subsequent maintenance with pemetrexed. Documented disease progression after 3rd maintenance cycle with pemetrexed; 2nd line therapy with pembrolizumab 200 mg every 3 weeks was implemented. At the 5th treatment cycle, the patient reported asthenia, anorexia and peripheral edema. The analytical study showed sCreat of 2.5 mg/dl (baseline sCreat - 0.8 mg/dl). The renal ultrasound excluded obstruction. Urinary sediment showed leukocyturia - 10 cells/field. It was observed by nephrology and after exclusion of other causes, the diagnosis of interstitial nephritis secondary to pembrolizumab, was considered. Treatment with pembrolizumab was suspended and prednisolone 1 mg/kg/day was instituted, and maintained full dose for 1 month (sCreat on this date: 1 mg/dl), with tapering over 3 months, with consequent clinical and analytical improvement. In these 3 months, the patient showed progression of the oncological disease. A 3rd-line therapy with docetaxel (75 mg/m^2) and nintedanib (200 mg, twice daily) every 3 weeks for 4 cycles was started. Subsequently, maintenance treatment with nintedanib was performed. Only renal biopsy would diagnose acute interstitial nephritis, but the clinical history of these patients, the urinary sediment and the response to the instituted treatment make the hypothesis very likely, so renal biopsy was not performed. No new renal complications were identified in these patients.

Discussion

Immune checkpoint inhibitors (ICPi) have become one of the most widely prescribed anticancer treatments nowadays [1].

ICPs increase antitumor immunity by blocking intrinsic down-regulators of immunity, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1) [2]. They are largely used for the treatment of several solid malignancies (such as advanced melanoma, advanced non-small cells and small cells lung cancer or urologic cancers).

Pembrolizumab is a highly selective monoclonal immunoglobulin G4-Kappa (IGg4-kappa) isotype antibody that binds to PD-1. In 2016, the Food and Drug Administration (FDA) approved pembrolizumab as a first-line monotherapy treatment in adult patients with untreated advanced non-small cell lung cancer with PD-L1 expression greater than 50% and lack of mutations [3]. However, by increasing immune system activity, ICPi can precipitate immune-related adverse events. The toxicity profiles of ICPs are heterogeneous and depend on their type, as well as, on their association with other ICPs, chemotherapy or a targeted therapy [4]. These drugs most commonly affect the skin, gastrointestinal tract, liver and endocrine system, but may involve any organ system, including the kidneys [5]. Data on the incidence and characteristics of nephrotoxicity from ICPi are limited and derived largely from small case series and oncologic studies. A recently published real-life study showed an incidence of ICP induced acute kidney injury (AKI) of 3.7% [4]. A median time of 9 months has been described between the start of therapy with pembrolizumab and the onset of acute kidney injury [6].

The current American Society of Clinical Oncology (ASCO) guidelines for the management of IRAE suggest that patients, receiving ICPi with sCr increase two to three times of baseline, should have ICPi held and received 0.5 to 1 mg/kg/day prednisone equivalents (with an increase to 1-2 mg/kg/day if worsening or with no improvement). It is recommended that clinicians manage grade 3 to 4 toxicities as follows: permanently discontinue ICPi, consult nephrology, evaluate for other causes (recent IV contrast, medications, fluid status, *etc*.), administer corticosteroids (initial dose of 1 to 2 mg/kg/d prednisone or equivalent). These guidelines also state that reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted [7].

A recent study showed that in cases of mild to moderate kidney injury, patients are responsive to temporary discontinuation of ICPi and to systemic corticosteroids for severe cases. Re-exposure with ICPi may be considered in these patients, particularly those with limited therapeutic options [5].

Conclusion

The growing use of immunotherapy in the treatment of cancer imposes the physician's attention to possible adverse effects. Despite the low incidence of adverse renal effects, their early identification and treatment are crucial. Monitoring renal function and early identification of acute renal lesion (AKI) is essential. The optimal management of ICP-induced AKI remains uncertain, and requires close collaboration between the pulmonology and nephrology departments.

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