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*Case Report*

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# *Hypereosinophilia with Renal Injury Caused by Immune Checkpoint Inhibitor*

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**Abstract**

This clinical case presents a 55-year-old man with a locally-advanced malignant kidney tumor. The patient receives a radical nephrectomy and adjuvant pembrolizumab. The patient develops hypereosinophilia with organ-specific kidney injury. By means of applying the Naranjo test, we concluded that this adverse event was caused by immunotherapy. So, we suspended immunotherapy and decided an early administration of corticosteroids, obtaining a complete recovery. Subsequently, we restarted pembrolizumab and it was not observed eosinophilia, urine eosinophils, or kidney damage again. In this regard, the eosinophilic interstitial nephritis caused by immunotherapy is rare. Therefore, this case report is important because it contributes to the scarce literature on the topic and provides a management guide for these cases based on the best available evidence.

**Keywords:** Eosinophil-induced adverse events; Eosinophilic interstitial nephritis; Immune checkpoint inhibitors; immune-related adverse events; Immune-related blood eosinophilia; Immunotherapy.

## Introduction

Programmed cell death protein-1 (PD-1) is a type 1 transmembrane protein of 50 to 55 kDa that is part of the immunoglobulin superfamily CD28/CTLA-4 [1]. This protein is expressed in hematopoietic cells in peripheral blood in the form of T and B lymphocytes, macrophages, and dendritic cells [1]. With respect to PD-1, it has two main ligands: the programmed death-ligand 1 and 2 (PD-L1 and PD-L2) [2].

PD-L1 is a type 1 transmembrane protein of 40 kDa that is widely expressed in lymphoid and non-lymphoid tissue and in antigen-presenting cells such as macrophages and dendritic cells [1]. PD-L1 has a regulatory function in the immune system because it inhibits the immune response. In this way, PD-L1 has a physiological function because it prevents the rejection of the embryo in pregnancy, decreases the rejection of tissue and organ transplants, reduces the exaggerated immune response against infections and decreases the development of autoimmune diseases.

However, PD-L1 can be significantly expressed in tumor cells and non-transformed cells in the tumor microenvironment, and PD-1 can be significantly expressed in tumor-infiltrating T lymphocytes. In this way, when the PD-L1 ligand of the tumor cell binds with its PD-1 receptor of the cytotoxic CD8 T lymphocyte, the activation, proliferation, and anti-tumor function of this CD8 T lymphocyte are inhibited, achieving tumor immune scape.

When the PD-L1 of the tumor cell binds with the PD-1 receptor of the T lymphocyte, the production of interleukin 2 and cell proliferation are inhibited in this lymphocyte. This is because the activation of PD-1 (by binding to its ligand) inhibits T-cell receptor

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(TCR) induced phosphorylation of the ZAP70/CD3ζ signalosome and downstream signaling to PKCθ. In this way, the inactivation of PKCθ (by attenuating the phosphorylation of the PKCθ loop) inhibits the activation of transcription factors NF-kB and the production of interleukin 2, which are stimulated by the TCR's antigenic recognition [3]. In addition, the activation of PD-1 in the T lymphocyte induces the expression of the ubiquitin ligase E3 CBL-b in this lymphocyte, causing the internalization and degradation of the TCR [4].

On the other hand, when PD-L1 binds to its receptor, it is activated and favors a cascade of intracellular signaling in the tumor cell, causing the activation of the mTOR metabolic pathway, which in turn favors the survival and growth of the tumor cell [5]. Also, the intracellular signaling produced by the activation of PD-L1 allows the neoplastic cell to be protected from pro-apoptotic signals such as Fas-FasL binding and the action of interferons [6,7].

Using this basic knowledge, researchers have developed a series of monoclonal antibodies that bind to PD-1 (pembrolizumab, nivolumab and cemiplimib) or PD-L1 (atezolizumab, avelumab and durvalumab) [1]. Thus, these drugs prevent the binding of the receptor to its ligand and the subsequent inhibition of the specific cellular tumor response. This family of drugs together with ipilimumab (CTLA-4 cytotoxic T-lymphocyte-associated antigen 4 inhibitors [8,9] are called immune checkpoint inhibitors (ICIs).

Currently, these ICIs are widely used in advanced cancers such as melanoma, lung carcinoma, urothelial carcinoma, renal carcinoma, squamous cell carcinoma of the head and neck and/or Hodgkin's lymphoma [10]. These drugs are even increasingly being prescribed in the adjuvant setting, such as in melanoma, non-small cell lung carcinoma and/or digestive cancers [11-14], in the perioperative period in the case of triple negative breast carcinoma [15], and even in neoadjuvant therapy, as in the case of non-small cell lung carcinomas [16].

However, ICIs frequently cause immune-related adverse events (irAEs) that mainly involve the intestine, skin, endocrine glands, liver and/or lungs, but that can potentially affect any tissue. In addition, irAEs can become fatal [17].

In this context, this article aims to present a clinical report of a rare complication associated with pembrolizumab type hypereosinophilia with specific organ damage at the renal level.

We think this study is important because it contributes to reinforce the scarce literature on this adverse event related to immunity. In addition, ICIs are widely effective. Therefore, these drugs will increasingly be applied in clinical practice. Therefore, medical oncologists must learn to diagnose these complications early and to manage them with expertise.

## Case report

55-year-old male who presents gross hematuria. The patient has a history of stage 1 chronic arterial hypertension treated with valsartan (ARA II). The patient is eutrophic, has no other comorbidities, and has no personal or family history of neoplasms. The following laboratory results are all normal: blood count, fasting blood glucose, plasma electrolytes, coagulation factors, and renal, hepatic, and thyroid function.

Chest, abdomen, and pelvis scan shows a 5-centimeter diameter mass at the upper pole of the right kidney with no distant metastatic.

We performed a right radical nephrectomy. Histology shows a low-grade clear cell carcinoma, according to the simplified Fuhrman classification [18], with extension to the perirenal fat and involvement of a hilar lymph node. We diagnosed a stage III right renal carcinoma pT3apN1M0 (according to the eighth edition of the American Joint Committee on Cancer) [19].

Subsequently, we prescribed adjuvant therapy with pembrolizumab based on the best available evidence [20].

At 6 weeks into adjuvant therapy, there was a newly appearing hypereosinophilia (defined as eosinophils in blood higher than 1,500 cells/microliter) and acute kidney injury (AKI) with rapid, progressive, and proportional increase in blood urea nitrogen and creatinine (renal-type injury), along with the detection of eosinophils in urine. In fact, the creatinine level was elevated from a baseline of 0.9 to 2.5 mg/dl and there was a moderate deterioration in calculated creatinine clearance (clearance of 104 decreased to 37.8 ml/min/$m^2$).

We decided to hospitalize the patient to achieve a better study and management of this pathology.

In the differential diagnosis of the causes of eosinophilia, a focused medical history ruled out any patient history of allergies, bronchial asthma, or atopy. Skin tests for immediate hypersensitivity and food allergies were negative. Stool parasite testing and serology for parasitic infections ruled out helminthiasis as the cause of eosinophilia.

In the study of AKI, we ruled out other potential causes such as dehydration, urinary tract infection or obstructive urinary pathology. In addition, we decided to discontinue valsartan to avoid aggravating the renal failure and to prevent the onset of hyperkalemia. We replaced this antihypertensive agent with nitrendipine (voltage-dependent calcium channel blocker), achieving good management of the patient's blood pressure values.

Also, although American Society of Clinical Oncology (ASCO) recommends starting corticosteroids without performing a renal biopsy [21], we believe it is challenging to make a differential diagnosis of AKI caused by immunotherapy as opposed to another potential cause [22]. In addition, the overdiagnosis of irAEs leads to the unnecessary discontinuation of an effective therapy and unnecessary adverse effects from corticosteroid use [22]. Therefore, in the absence of an absolute contraindication and any other potential cause of the AKI, renal biopsy is very useful in guiding the correct treatment [22]. Therefore, we completed the study of the AKI with a percutaneous renal biopsy. In our case, histology confirmed the diagnosis of eosinophilic interstitial nephritis.

Therefore, we conclude that this organ-specific eosinophilia with renal damage is an irAE produced by pembrolizumab.

In addition, tests were ordered to rule out injury to other organs due to eosinophilic infiltration:

a) A general and thorough skin examination ruled out eosinophil skin lesions.

b) The normal electrocardiogram and echocardiogram plus a normal troponin I and brain natriuretic peptide discarded the possibility that the patient was experiencing eosinophilic myocarditis.

c) A normal blood gas and a normal chest scan ruled out eosinophilic pneumonitis.

d) A normal liver profile and an abdominal scan ruled out eosinophilic cholangitis.

We discontinued immunotherapy and decided an early oral administration of prednisone at a dose of 0.5 mg/kg/day. This allowed 100% resolution of the clinical picture within 3 days.

After the period of 1 week, we progressively tapered off the corticosteroid until it was discontinued. Blood eosinophil values and renal function remained normal. There was no new presentation of eosinophils in urine samples. Therefore, we discharged the patient with instructions for periodic and strict follow-up.

In addition, we decided to restart pembrolizumab because the risk-to-benefit ratio justifies it. This is because we determined the patient's acute eosinophilic interstitial nephritis to be of moderate severity, and because adjuvant immunotherapy in renal cancer is beneficial (progression-free survival is significantly greater with pembrolizumab versus placebo) [20]. After 6 cycles of pembrolizumab, the clinical picture has not been reactivated, there has been no recurrence of eosinophilia, and imaging does not show neoplastic relapse.

**Table 1:** Naranjo's algorithm applied to this clinical case.

| Ask | yes | not | Does not apply | answer |
|---|---|---|---|---|
| Number 1 | 1 | 0 | 0 | 1 |
| Number 2 | 2 | -1 | 0 | 2 |
| Number 3 | 1 | 0 | 0 | 1 |
| Number 4 | 2 | -1 | 0 | -1 |
| Number 5 | -1 | 2 | 0 | 2 |
| Number 6 | 1 | 0 | 0 | 0 |
| Number 7 | 1 | 0 | 0 | 0 |
| Number 8 | 1 | 0 | 0 | 0 |
| Number 9 | 1 | 0 | 0 | 1 |

**Total score 6**

Unlikely: 0 Possible: 1-4 Likely: 5-8 Definitive: Greater than or equal to 9.
Ask 1: Are there conclusive previous reports about this adverse reaction?
Ask 2: Did the adverse reaction appear after the suspected drug was administered?
Ask 3: Did the adverse reaction improve when the drug was discontinued treatment or when an antagonist was administered specific?
Ask 4: Did the adverse reaction recur when it was reintroduced administer the drug?
Ask 5: Are there other causes (other than administration of the drug) that may themselves have caused the reaction?
Ask 6: Has the drug been detected in the blood (or other humors) in a concentration whose toxicity is acquaintance?
Ask 7: Did the severity of the reaction increase with increasing dose or decreased by reducing it?
Ask 8: Did the patient have a similar reaction to it drug or analogous drugs at any exposure previous?
Ask 9: Was the adverse event confirmed by objective evidence?

## Discussion

In this clinical case, we diagnosed a hypereosinophilia-type irAE with specific renal damage. It is rare for such an adverse event to be caused by pembrolizumab. In fact, Bernard Tessier et al. recorded a low prevalence of 2.8% for eosinophilia as causing irAE, with a median maximum range of 1,000 eosinophils/microliter [23].

Therefore, we decided to apply the Naranjo test [24], which studies the probability of causality between adverse reactions and drugs [25]. When applying the test to our case, we obtained a score of 6, i.e., it is likely that the ICI is the cause of eosinophilia with specific renal injury (Table 1).

On the other hand, in a French observational study (n=37), for cases that did not present eosinophilia prior to the use of immunotherapy, it was found that the time of onset of moderate to severe immune-related blood eosinophilia (Eo-ir) from the start of immunotherapy is early (median of 6 weeks) and the maximum value of eosinophilia occurred with a median of 15 weeks. In addition, an Eo-ir was described in 32% of the cases and organ dysfunction due to eosinophilia in 57% of the cases. In this regard, the most common organ damage due to eosinophilia was skin damage. Renal injury was less common [26]. We must emphasize that an absolute eosinophil count (AEC) above normal values is not an index of severity by itself. In fact, this study included 7 cases with eosinophilia prior to the use of immunotherapy, and of these cases, in only 1 case was an eosinophil-induced adverse event (Eo-irAE) reported [26]. Therefore, the presence of eosinophilia prior to the use of an ICI is a predictor of a good response, greater progression-free survival, and overall survival with immunotherapy [27,28]. Moreover, in this French study, the highest median AEC was observed in asymptomatic patients and not in cases that presented Eo-irAEs. It is worth noting that the maximum AEC and the newly emerging Eo-irAEs are not correlated variables [26].

Just as eosinophilia prior to the use of immunotherapy is a predictor of a good response with this therapy, it has also been reported that new-onset eosinophilia during treatment with ICIs is a predictor of a good response, greater progression-free survival, and greater overall survival with immunotherapy [29].

Regarding the treatment of Eo-irAEs, the gold-standard for therapy is the early use of corticosteroids. When applying the recommendations of experts to our clinical case, we have to [21,30,31]:

a) Administer prednisone 0.5 to 1 mg/kg/day for mild to moderate renal injury due to eosinophilia. If moderate injury persists for more than 1 week, administer prednisone/methylprednisolone 1 to 2 mg/kg/day.

b) Administer prednisone/methylprednisolone 1 to 2 mg/kg/day for severe renal injury due to eosinophilia. If the case no longer responds to corticosteroids, the use of immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, infliximab, or mycophenolate) is recommended.

Finally, in relation to the prognosis of Eo-irAEs, these are generally mild to moderate, and a complete or partial response is observed when ICIs are discontinued and when the use of corti-

costeroids is begun [26]. Cases of non-response to corticosteroids are very rare.

## Conclusions

We can conclude from this clinical case and the bibliographic review:

a) Eo-ir is rare. However, if it does occur, it occurs early [26]. Therefore, when using ICIs, it should be monitored with a monthly blood count.

b) In the presence of Eo-ir, the target organs must always be closely monitored for possible lesions, above all for eosinophilic myocarditis. This is because it is initially asymptomatic; however, myocardial damage can progress to irreversible heart failure or death [26].

c) In the presence of Eo-ir and Eo-irAEs, a differential diagnosis must always be made in order to optimize the decision-making process.

d) Eosinophilia prior to the use of ICIs or as a product of immunotherapy without organic injury is a predictor of a positive response with immunotherapy. This is because eosinophils contribute to the immune response against the tumor [32,33]. Therefore, we believe that in these cases the ICI should not be suspended. However, the possibility of target organ damage should be closely monitored.

e) The gold-standard of AKI by ICIs treatment is corticosteroids. An early initiation of this therapy (before 3 days) provides a higher probability of renal recovery when compared to a later initiation (after 3 days) [34]. In addition, short-term corticosteroid therapy (less than 28 days) leads to a degree of renal recovery that is similar to the recovery obtained with a prolonged therapy (29-84 days) [35].

f) After an Eo-irAE, if the clinical benefit is significant, we believe that immunotherapy should be restarted with caution. However, we suggest permanently suspending the ICIs in the following cases:

1) A severe Eo-irAE (grade III or greater) [21].

2) The rare cases of non-response to corticosteroids.

3) The rare cases of corticosteroid dependency. In particular, if more than 10 mg/day of prednisone is required, because at such doses the corticosteroid inhibits the action of ICI [36].

Finally, if we apply the thinking of Thomas Kuhn [37], ICIs have changed the therapeutic paradigm in clinical oncology. Therefore, as medical oncologists, we must be prepared to manage the complications of immunotherapy with expertise. For this reason, this article aims to contribute to the scarce literature on Eo-irAEs.

**Abbreviations:** PD-1: Programmed cell death protein; kDa: kilodalton; CD28: Cluster of differentiation 28 is one of the proteins expressed on T cells that provide co-stimulatory signals required for T cell activation and survival; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4, also known as CD152 (cluster of differentiation 152), is a protein receptor that functions as an immune checkpoint and downregulates immune responses; PD-L1: Programmed death-ligand 1; PD-L2: Programmed death-ligand 2; CD8: Cluster of differentiation 8 is a transmembrane glycoprotein that serves as a co-receptor for the T-cell receptor (TCR). Along with the TCR, the CD8 co-receptor plays a role in T cell signaling and aiding with cytotoxic T cell-antigen interactions; TCR: T-cell receptor; ZAP70: Zeta-chain-associated protein kinase 70 is a protein normally expressed near the surface membrane of lymphocytes (T cells, natural killer cells, and a subset of B cells); CD3ζ = homodimer-forming type 1 transmembrane protein and is part of the T-cell antigen receptor (TCR-CD3) complex along with TCRαβ, CD3γε, and CD3δε dimers expressed on the surface of T cells. NF-kB: Nuclear factor kappa light chain enhancer of activated B cells is a protein complex that controls deoxyribonucleic acid transcription; CBL-b: + Casitas B lymphoma-b is a E3 ubiquitin ligase. This has been identified as a critical regulator of adaptive immune responses; mTOR: mammalian Target of Rapamycin is a protein present in the cells of mammalian animals that has important functions in the regulation of growth, proliferation, and cell death; Fas: Death receptor on the surface of cells that leads to programmed cell death (apoptosis) if it binds to its ligand, Fas ligand; FasL: Fas ligand; ICIs: Immune checkpoint inhibitors; irAEs: Immune-related adverse events; ARA II: Angiotensin II AT1 receptor antagonist; AKI: Acute kidney injury; mg/dl: Milligram/deciliter; ml/min/$m^2$: Milligram/minute/square meter; ASCO: American Society of Clinical Oncology; irAE: Immune-related adverse event; mg/kg/day: milligram/kilogram/day; ICI: Immune checkpoint inhibitor; Eo-i: Immune-related blood eosinophilia; AEC: absolute eosinophil count; Eo-irAE: Eosinophil-induced adverse event; Eo-irAEs: Eosinophil-induced adverse events; mg/day: Milligram/day.

**Conflicts of interest:** The authors declare that they have no conflicts of interest.

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