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Case Report

Pembrolizumab-associated acute tubular interstitial nephritis with asymptomatic serum creatinine elevation: A case report

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Abstract

Immune checkpoint inhibitors (ICPIs) have transformed cancer treatment but may cause immune-related adverse events (irAEs) affecting multiple organ systems. Renal irAEs, particularly tubulointerstitial nephritis (TIN), are uncommon yet clinically significant, and their optimal diagnosis and management — including the decision to rechallenge — remain areas of active investigation.

A 59-year-old male with metastatic lung adenocarcinoma and high PD-L1 expression (TPS 80%) received pembrolizumab monotherapy. After eight cycles, asymptomatic acute kidney injury (AKI; serum creatinine 2.97 mg/dL) was detected during routine monitoring. Clinical and laboratory evaluation — including peripheral eosinophilia and pyuria with leukocyte casts on urine microscopy — supported a diagnosis of TIN without recourse to kidney biopsy. The Naranjo Adverse Drug Reaction Probability Scale score was 8, indicating a probable association with pembrolizumab. Prednisolone was initiated, and serum creatinine returned to baseline within 5 days. Following complete renal recovery and a joint oncology–nephrology risk–benefit assessment, pembrolizumab was successfully rechallenged. The patient completed 12 additional cycles with stable renal function and no recurrence of AKI.

This case demonstrates that pembrolizumab-associated TIN may present as entirely asymptomatic creatinine elevation, underscoring the importance of routine biochemical monitoring. A biopsy-free diagnostic approach was feasible when clinical and laboratory findings were concordant. The successful rechallenge outcome contributes to the limited evidence supporting individualized ICPI resumption following grade 3 renal irAEs.

Keywords: Pembrolizumab, Immune-related adverse events, Acute tubulointerstitial nephritis, Acute kidney injury, Rechallenge, Lung adenocarcinoma

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INTRODUCTION

The immune checkpoint inhibitors (ICPIs) are monoclonal antibodies that target inhibitory receptors on T cells, other immune cells, and tumor cells (1, 2). However, treatment-related primary and acquired resistance and side effects are crucial problems (3–5). The most important side effects of immunotherapy treatment are immune-related adverse events (irAEs), which are autoimmune conditions that can be seen in all organs. Renal side effects are relatively less frequent, although gastrointestinal, skin, and endocrine irAEs are more common (5). Awareness, early diagnosis, and treatment are essential for toxicities that can be seen in almost all organs at any stage of treatment. We report a case of tubulointerstitial nephritis associated with immunotherapy (pembrolizumab) diagnosed and treated without renal biopsy.

CASE REPORT

A 59-year-old male patient presented to Cukurova University Faculty of Medicine, Department of Medical Oncology, without any documented comorbidities. He experienced right upper quadrant pain in July 2023. A thorax tomography showed a 62×54 mm consolidation area that was continuous with the bronchus in the upper part of the right lower lobe. The biopsy revealed that the condition was lung adenocarcinoma. PET/CT showed bone metastases, a lesion in the left adrenal gland, lymphadenopathy in the right lower paratracheal, subcarinal/subcarinal right paraesophageal, and right hilar regions. No driver mutation was identified. The PD-L1 Tumor Proportion Score (TPS) was 80%. The patient commenced treatment with pembrolizumab 200 mg on July 7, 2023, every 3 weeks (q3w). Baseline laboratory findings at the time of immunotherapy initiation are summarized in **Table 1**; all parameters were within normal reference ranges. Hypothyroidism was diagnosed 3 months after pembrolizumab treatment was initiated (October 2023, TSH: 96 mIU/L). Levothyroxine 100 mcg was started. Pembrolizumab treatment was continued under levothyroxine treatment. TSH level became normalized.

Table 1. Baseline Laboratory Findings at Immunotherapy Initiation (July 2023)

Parameter	Value	Reference Range
Biochemistry		
Serum creatinine	0.90 mg/dL	0.70–1.20 mg/dL
Blood urea nitrogen (BUN)	16 mg/dL	6–20 mg/dL
Aspartate aminotransferase (AST)	24 U/L	0–40 U/L
Alanine aminotransferase (ALT)	28 U/L	0–41 U/L
Albumin	4.1 g/dL	3.5–5.2 g/dL
Thyroid stimulating hormone (TSH)	1.45 mIU/L	0.4–4.0 mIU/L
Hematology		
Hemoglobin	13.4 g/dL	13.0–17.5 g/dL
White blood cell count (WBC)	$6.80 \times 10^3/\mu L$	$4.00–10.00 \times 10^3/\mu L$
Neutrophils	$4.10 \times 10^3/\mu L$	$2.00–7.00 \times 10^3/\mu L$
Eosinophils	$0.12 \times 10^3/\mu L$	$0.00–0.50 \times 10^3/\mu L$
Platelets	$265 \times 10^3/\mu L$	$150–450 \times 10^3/\mu L$
Urinalysis		
Protein	Negative	Negative
Leukocyte esterase	Negative	Negative
Erythrocytes	0–1 /HPF	0–3 /HPF
Leukocytes	0–1 /HPF	0–5 /HPF

The patient, who had completed eight cycles of treatment, presented for the ninth cycle on February 22, 2024, for routine examinations. Despite the patient's lack of complaints, we detected acute renal failure (serum creatinine 2.97 mg/dL, Figure 1). Postrenal obstruction was excluded with USG. At the time of AKI detection, the patient's only concomitant medication was levothyroxine for pembrolizumab-associated hypothyroidism. Notably, no medications commonly implicated in drug-induced acute interstitial nephritis — including proton pump inhibitors, nonsteroidal anti-inflammatory drugs, and antibiotics — were being administered. The complete blood count revealed the presence of eosinophilia (Figure 2). The 24-hour urine protein excretion was 647 mg/day. Urine microscopy demonstrated pyuria with leukocyte casts, findings suggestive of acute interstitial nephritis (Figure 3).

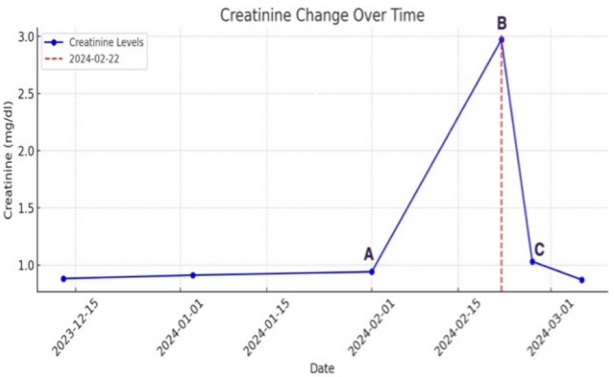

Figure 1. Serial serum creatinine levels during pembrolizumab treatment, showing the rise at the time of acute kidney injury detection and subsequent recovery following corticosteroid therapy.

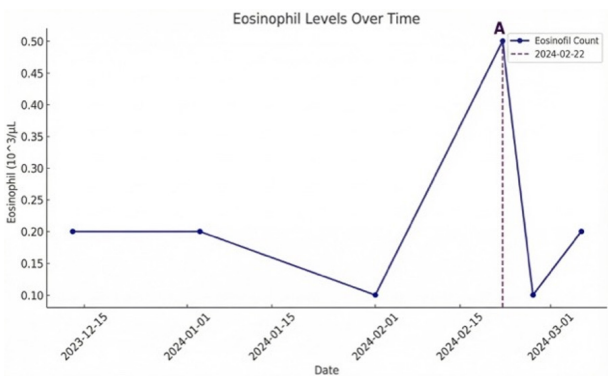

Figure 2. Eosinophil kinetics during the course of treatment. **(A)** Peak eosinophil count concurrent with acute kidney injury onset. **(B)** Trend of absolute eosinophil count over time, demonstrating normalization following pembrolizumab discontinuation and corticosteroid initiation.

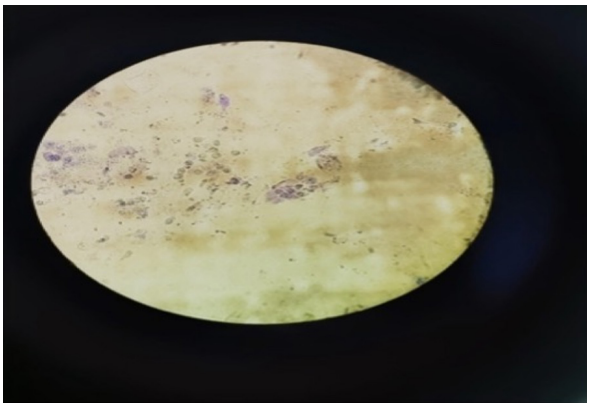

Figure 3. Urine microscopy demonstrating pyuria with leukocyte casts, findings supportive of acute interstitial nephritis.

The pembrolizumab treatment for the patient was discontinued. We initiated prednisolone at a dose of 32 mg/day (approximately 0.5 mg/kg based on the patient's body weight of 65 kg). Although this dose was lower than the 1 mg/kg/day recommended by current guidelines, the decision was based on clinical judgment given the patient's asymptomatic presentation and hemodynamically stable condition. Serum creatinine declined from 2.97 mg/dL to 1.03 mg/dL within approximately 5 days, indicating a prompt and complete response. A week later, we determined the creatinine levels to be 0.91 mg/dL. Following the treatment with prednisolone, eosinophil counts returned to normal range. The daily dose of prednisolone was reduced to 16 mg after two weeks and to 8 mg after one week, and subsequently discontinued.

Following complete renal recovery and discontinuation of prednisolone, the patient resumed his ninth cycle of pembrolizumab treatment on March 19, 2024, at a dosage of 200 mg q3w. The rechallenge decision was made jointly by the treating oncologist and a consulting nephrologist after careful risk–benefit assessment. Serum creatinine was monitored before each subsequent cycle. As of December 2024, the patient has received 12 additional cycles with stable renal function and no recurrence of AKI.

DISCUSSION

Immunotherapies have entered clinical use in many solid and hematologic tumors, particularly melanoma, lung cancer, and kidney cancer. irAEs are frequently observed between weeks 2 and 16 depending on the organ in which they develop. However, it should be kept in mind that they may occur at any period of treatment or even up to 1 year after treatment is discontinued. Compared to monotherapy, there is a higher incidence of irAEs with combination therapy. In our case, acute renal failure was detected about 7 months after starting pembrolizumab. Interestingly, the patient had no complaints and it was detected during routine follow-up visits.

Renal side effects associated with immunotherapy are less common and there are some problems with the definition of acute kidney injury (AKI). Kidney Disease: Improving Global Outcomes Working Group (KDIGO) consensus criteria define acute kidney failure based on relative changes in serum creatinine levels. For example, an increase of up to 1.5 times the upper limit of normal for creatinine increase is defined as grade 1. However, muscle wasting may occur in cancer patients and significant increases in serum creatinine levels may be considered "normal". In addition, conditions requiring hospitalization for AKI are defined as grade 3, while there are no defined criteria for grades 1 and 2 (6–11).

The prevalence of immune checkpoint inhibitor–associated acute kidney injury (ICPIs-AKI) is predicted to be between 1.4% and 4.9%. Tubulointerstitial nephritis (TIN) was initially identified as the predominant renal lesion caused by immune checkpoint inhibitor (ICPI) therapy. However, other immune-mediated diseases, such as different types of glomerulonephritis, have also been documented (12). Acute kidney injury (AKI) occurred at a median of 14 weeks (interquartile range [IQR], 6–37) following the commencement of immune checkpoint inhibitor (ICPi) treatment, and 2 weeks (IQR, 2–3) after the last dose of ICPi. The severity of AKI was classified as stage 2 in 43% of patients, stage 3 in 57% of patients, and 9% of patients required renal replacement therapy (RRT). In 43% of instances, an extrarenal immune-related adverse event (irAE), typically a rash, occurred either before or at the same time as acute kidney injury (AKI) (12). The occurrence of pembrolizumab-related tubulointerstitial nephritis (TIN) in our case was similarly in line with the existing literature. AKI in cancer patients can be caused by dehydration, infection, adverse drug reaction, contrast and analgesic nephropathy, tumor lysis syndrome, or postrenal obstruction. Acute interstitial nephritis (AIN) is the most common pathology. Other pathologies include glomerular diseases such as minimal change disease, acute tubular necrosis (ATN), and thrombotic microangiopathy. ICPIs rarely lead to the development of glomerular disease. Patients who develop minimal change disease, focal segmental glomerulosclerosis, or membranous nephropathy often present with nephrotic syndrome (13–17). The Naranjo Adverse Drug Reaction Probability Scale score in our case was 8, indicating a probable adverse drug reaction (18). Detailed item-by-item scoring with explicit justification is provided in **Supplementary Table 1**. The patient's concurrent hypothyroidism also provides evidence for pembrolizumab-associated TIN.

The gold standard for the diagnosis of ICPI-related glomerular diseases and AKI is a kidney biopsy. However, a kidney biopsy may not always be necessary. All causes of AKI should be ruled out in the differential diagnosis (5). In our case, there was no evidence of dehydration among the possible causes of AKI, postrenal causes were excluded by abdominal USG, and the patient was not receiving any concomitant nephrotoxic medications or drugs commonly associated with acute interstitial nephritis, such as proton pump inhibitors, nonsteroidal anti-inflammatory drugs, or antibiotics. Platelet count and coagulation parameters were within normal limits; thus, the decision to forgo kidney biopsy was not attributable to procedural contraindications. Rather, the combination of temporal association with

pembrolizumab, peripheral eosinophilia, pyuria with leukocyte casts on urine microscopy, the systematic exclusion of alternative etiologies, and the concurrent presence of another irAE (hypothyroidism) provided sufficient diagnostic confidence for pembrolizumab-associated tubulointerstitial nephritis without histological confirmation.

Guidelines recommend discontinuation of treatment in case of grade 2 or higher toxicity.

Supplementary Table 1. Adverse Drug Reaction Probability Scale (Naranjo Algorithm Assessment)

Scoring interpretation: ≤0 = Doubtful; 1–4 = Possible; 5–8 = Probable; ≥9 = Definite

No.	Question	Yes	No	Do not know	Score	Justification
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1	Pembrolizumab-associated TIN has been reported in multiple published studies (Cortazar et al., 2020; Gupta et al., 2020).
2	Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2	AKI was detected after 8 cycles of pembrolizumab (approximately 7 months after initiation).
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1	Serum creatinine improved from 2.97 to 1.03 mg/dL within 5 days of pembrolizumab discontinuation and corticosteroid initiation.
4	Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	0	AKI did not recur during 12 additional cycles of rechallenge; scored as "Do not know" to reflect uncertainty regarding influence of monitoring protocol.
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2	Dehydration, infection, nephrotoxic drugs, contrast nephropathy, and postrenal obstruction were systematically excluded.
6	Did the reaction reappear when a placebo was given?	−1	+1	0	0	No placebo was administered.
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0	Pembrolizumab serum levels were not measured; therapeutic drug monitoring is not standard practice for ICPIs.
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0	Dose was not modified; pembrolizumab was administered at the standard flat dose of 200 mg throughout.
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	+1	The patient developed pembrolizumab-associated hypothyroidism (another irAE) 3 months after treatment initiation.
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1	Elevated serum creatinine (2.97 mg/dL), peripheral eosinophilia, pyuria with leukocyte casts, and proteinuria.
					Total = 8	**Probable adverse drug reaction**

Corticosteroids are recommended as initial treatment, although the specific dosage may differ between treatment guidelines. However, when toxicity decreases to grade 1, nearly all guidelines recommend a progressive reduction in corticosteroid dosage. Approximately 85% of patients with AKI respond to corticosteroids with partial or complete improvement. Patients who fail to recover within

one week should be closely monitored, and alternative immunosuppressive agents such as cyclophosphamide, azathioprine, cyclosporine, infliximab, or mycophenolate mofetil should be contemplated (4). In our case, AKI improved on the 5th day of corticosteroid treatment despite an initial prednisolone dose (0.5 mg/kg/day) that was lower than the guideline-recommended 1 mg/kg/day. The rapid and complete renal recovery observed with this lower dose may suggest that not all patients with grade 3 ICPI-associated AKI require full-dose corticosteroid therapy, although this observation from a single case warrants further investigation.

Patients who develop AKI in conjunction with irAEs also have their treatment interrupted, and in certain cases, it is entirely discontinued. The ASCO guideline advises permanent discontinuation of ICPIs in patients who experience grade 3 or higher renal toxicity (3). Nevertheless, this recommendation must be weighed against individual clinical circumstances, particularly when limited therapeutic alternatives exist. In the present case, the decision to rechallenge with pembrolizumab was made jointly by the treating oncologist and a consulting nephrologist following a comprehensive risk–benefit assessment. Several patient-specific factors supported this decision: first, complete recovery of renal function to baseline values (serum creatinine 0.91 mg/dL) following corticosteroid therapy; second, the achievement of stable disease under pembrolizumab, indicating ongoing clinical benefit; third, the absence of actionable driver mutations and high PD-L1 expression (TPS 80%), which rendered pembrolizumab monotherapy the most appropriate and practically the only viable systemic treatment option; and fourth, the successful completion of the full corticosteroid taper prior to rechallenge, suggesting resolution of the immune-mediated process. To mitigate the risk of recurrent nephrotoxicity, serum creatinine was monitored before each subsequent pembrolizumab cycle. Reassuringly, the patient completed 12 additional cycles without recurrence of AKI, with stable renal function maintained throughout. Although AKI recurrence has been reported in 8–40% of patients who undergo ICPI rechallenge (10, 19), our experience adds to the growing evidence that carefully selected patients with complete renal recovery may safely resume ICPI therapy under close monitoring.

CONCLUSION

This case illustrates that pembrolizumab-associated tubulointerstitial nephritis may present with entirely asymptomatic serum creatinine elevation, reinforcing the necessity of routine biochemical monitoring at each treatment cycle. The combination of peripheral eosinophilia, pyuria with leukocyte casts, and the exclusion of alternative etiologies enabled a confident clinical diagnosis without recourse to kidney biopsy, allowing prompt initiation of corticosteroid therapy. Furthermore, the successful rechallenge with pembrolizumab — undertaken through a joint oncology–nephrology decision following complete renal recovery — demonstrates that carefully selected patients may safely resume ICPI therapy under close surveillance. These findings contribute to the limited but growing evidence base guiding the management of ICPI-associated renal toxicity in clinical practice.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: M.M.K., E.B., Design: M.M.K., E.B., B.S., Supervising: İ.O.K, B.S., Financing and equipment: B.K, Data collection and entry: M.M.K., E.B., T.K., Analysis and interpretation: M.M.K., E.B., T.K., Literature search: M.M.K., E.B., T.K., Writing: M.M.K., E.B., Critical review: İ.O.K., B.Ş., B.K., If else:

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