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Extranodal NK/T-cell lymphoma: a case report of renal insufficiency during PD1 inhibitor treatment

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Abstract. – BACKGROUND: Extranodal NK/T-cell lymphoma (ENKTL) is a subtype of non-Hodgkin's lymphoma that accounts for approximately 3-8% of all malignant lymphomas. So far, ENKTL has no standard treatment guidelines, and the current treatment methods pose adverse effects. The combination of programmed death receptors (PD-1) and programmed death receptors' ligands (PD-L1) downregulates effector T cells; hence, it may be an effective treatment for NK/T-cell lymphoma. Here, we report a patient diagnosed with ENKTL whose health was significantly improved after PD-1 immunotherapy. At the same time, the patient suffered from related renal toxic side effects. Immunotherapy is an emerging treatment method for tumors, and the early diagnosis and identification of its side effects are vital for the diagnosis and treatment of tumors.

CASE REPORT: Laboratory tests, pathological examinations, and the patient's history were performed to estimate the severity and the cause of renal insufficiency. The patient with ENKTL developed transient renal damage during immunotherapy. During the next treatment and examination, renal insufficiency was irrelevant to PD-1 inhibitors and avoided unnecessary drug withdrawal.

CONCLUSIONS: In the present case report, we discuss a patient who developed a severe transient renal impairment during immunotherapy and review published studies regarding immunotherapy and its renal-related side effects. We also outline how to critically distinguish whether a patient's kidney injury is anti-PD-1 treatment. We also provide insights to oncologists to develop an effective follow-up treatment plan for early detection and management of any anti-PD-1 treatment side effects.

Key Words:
ENKTL, Immune therapy, PD-1, PD-L1, Renal insufficiency.

Case Report

A 44-year-old male patient arrived in our hospital with a sore throat and 38°C fever in September 2018. The patient did not experience any headaches, dizziness, cough, or expectoration. Nasopharyngoscopy revealed new neoplasms in the nasopharynx and oropharynx. The pathology test of nasopharynx biopsy revealed flaky necrosis, inflammatory exudation, and few atypical lymphoid cell proliferations. Immunohistochemistry showed PCK (+), CD20 (-), CD3p (+), CD3 (+), CD5 (-), CD56 (+), TIA-1 (+), granzyme B (+), CD30 (+, P), S-100 (-), ALK-1 (-), Ki67/MIB-1 (+, approximately 70%), and EBER1/2-ISH (+). Genetic rearrangements indicated a low amplification peak of T cell receptor-γ genes (TCRG), supporting a diagnosis of EB virus-associated lymphoproliferative disorders, particularly extranodal NK/T-cell lymphoma (ENKTL), nasal type. PET-CT scanning revealed an increased glucose metabolism in the bilateral nasopharynx, posterior oropharyngeal wall, and right adrenal gland with maximum SUV values of 11.76 and 11.03, respectively (Figure 1a). Blood work and liver and kidney function were normal. Thus, the patient's diagnosis was extranodal nasal-type NK/T-cell lymphoma (stage IIIE).

After excluding contraindications, the patient was treated with two cycles of modified SMILE regimen chemotherapy on 2019-01-08 and 2019-1-30. The sore throat symptoms were not significantly alleviated after chemotherapy. Instead, the patient was found to have yellow-white pus moss attached to the posterior pharyngeal wall. However, the intermittent fever was treated with anti-in-

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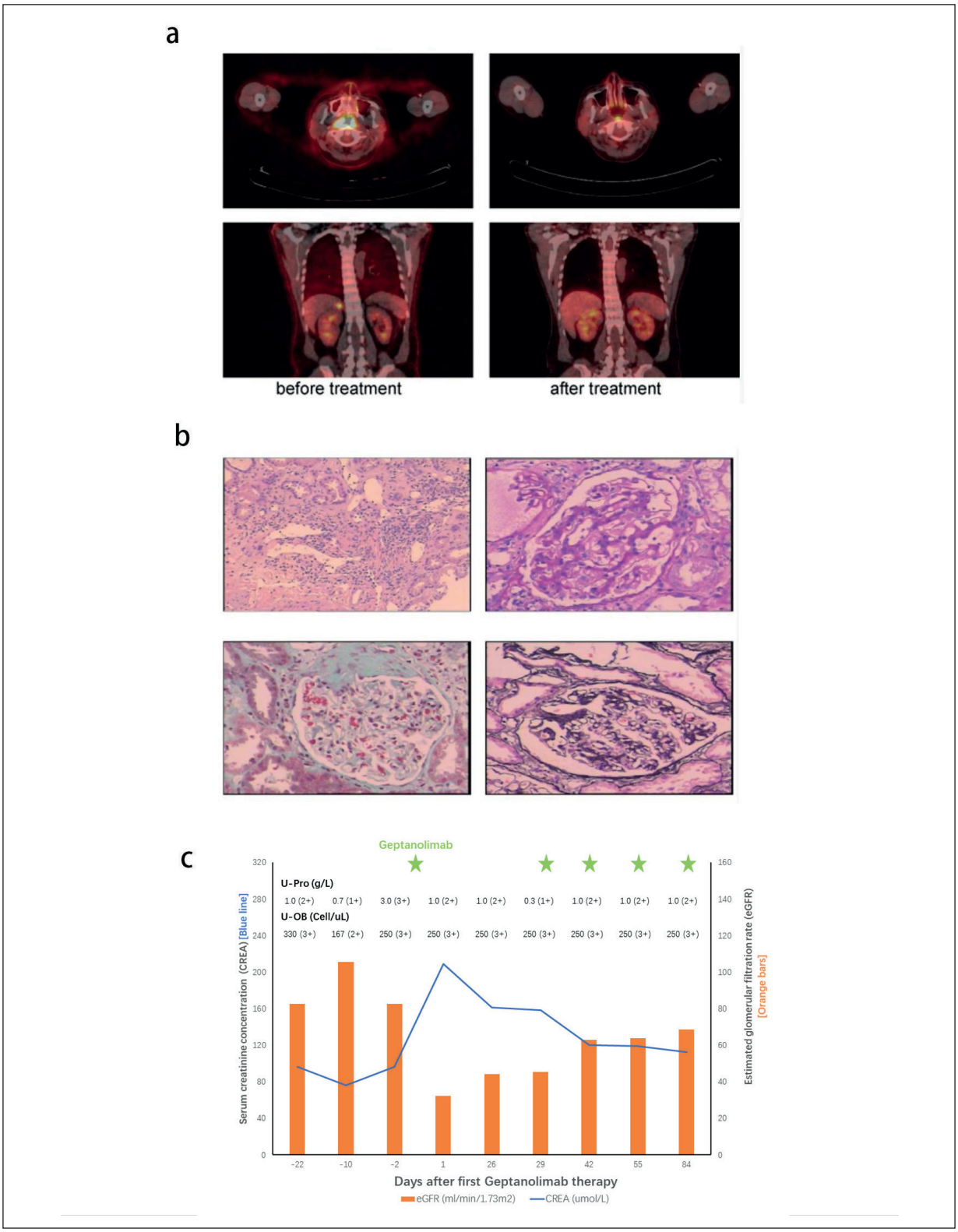

Figure 1. ***a***, A PET-CT revealing an increased glucose metabolism in the bilateral nasopharynx, posterior oropharyngeal wall, and right adrenal gland on 2019-03-12 before treatment; A PET-CT revealed an increased glucose metabolism in the posterior oropharyngeal wall on 2019-07-01 after treatment. **b**, Pathological results of renal biopsy indicate glomerular segmental mesangial hyperplasia, individual glomerular segmental sclerosis, and visible small crescent formation at magnifications ×100 and ×400). **c**, Changes in patient serum CREA and eFGR levels before and after treatment with a PD-1 inhibitor.

fection therapy. PET-CT re-examination revealed that the focal glucose metabolism levels in the posterior wall of the nasopharyngeal roof were increased with a maximum SUV value of 5.64 with no obvious abnormalities in the rest of the body (Figure 1a). Therefore, the efficacy of chemotherapy was evaluated as progressive disease (PD).

After a series of evaluations, the patient was enrolled in clinical trials and underwent programmed death receptor (PD-1) inhibitor therapy. His biochemical blood results conducted on 2019-3-31 revealed the presence of urea (UREA, 5.00 mmol/L), creatinine (CREA, 76.0 μmol/L), and an estimated glomerular filtration rate (eGFR) of 105.48 ml/min/1.73 m^2. In addition, urine tests indicated characteristic proteinuria, microhematuria, hemoglobin (103 g/L), and EBV DNA (1.45E+03 copies/mL). On 2019-4-10 at 11:00 a.m., the patient received an intravenous injection of 207 mg (3 mg/kg of body weight) Jeno mAb (PD-1 inhibitor) with rehydration, analgesia, and other symptomatic treatments.

On 2019-4-11 in the morning, the patient had a fever (40°C), no chills, stable vital signs, a urinary volume of 1000+ml/d, clear yellow urination, no urgency, dysuria, and no lower limbs and systemic edema. On 2019-4-11, routine blood re-examination and biochemical blood results showed 80 g/L hemoglobin and 85.6% neutral lobular granulocyte. The urine had 11.34*109/L neutral lobular granulocyte, 8.5 mmol/L UREA, 209.0 μmol/L CREA (Figure 1c), an estimated glomerular filtration rate (eGFR) of 32.3 ml/min/1.73 m2, and 384.0 μmol/L uric acid (URIC). Due to acute kidney damage, the patient was rehydrated and administered oral medicinal carbon tablets. Dexamethasone was not administered, and relevant examinations were performed to determine the cause of renal impairment.

The urinary color ultrasound revealed that the right kidney size was approximately 13.3×5.3×4.4 cm, and the left kidney size was approximately 12.0×4.3×5.1 cm. A sonogram of the renal parenchyma damage indicated double kidney growth. The urinary protein/creatinine was 0.163 g/mmol with an anti-glomerular basement membrane antibody assay (GBM) of 8.05 RU/ml, IgG of 20.7 g/L, IgA of 6.3 g/L, and KAP light chain of 17.8 g/L. Besides, LAM light chain was 11.6 g/L (Figure 1c). There were negative results for antinuclear antibody ANA (-), anti-double-stranded DNA antibody (-), anti-RNP antibody (-), and anti-SM antibody (-).

In 2019-5-7, the patient was subjected to pathological testing for renal biopsy, which indicated glomerular segmental mesangial hyperplasia, individual glomerular segmental sclerosis, and visible small crescent formation (Figure 1b). Electron microscopy revealed the presence of mesangial hyperplasia, mesenchymal deposition of electron-dense substance in the mesangial area, and the formation of a hump in the subepithelial lesion. Combined with immunofluorescence, we concluded the patient had IgA nephropathy (Figure 1c).

During this period, changes in renal function, electrolytes, and blood pressure were closely monitored. During the worst renal functioning period, the serum creatinine level reached 319.4 μmol/L, and the estimated glomerular filtration rate (eGFR) was 26.06 ml/min/1.73 m2 (2019-4-16) (Figure 1c). However, the patient gradually recovered, and the electrolyte blood pressure normalized. After ruling out renal damage caused by PD-1, infusions of Jeno mAb (3 mg/kg, once every two weeks) were resumed on 2019-5-10.

The patient's renal function was restored, his sore throat was relieved, and he no longer suffered from fevers. CT examination indicated that the nasopharyngeal, oropharynx and right adrenal masses were smaller. Moreover, the efficacy of the immunotherapy was established as a partial response (PR). The patient is currently under post-therapy follow-up for 24 months and is in recovery.

Discussion

In recent years, major breakthroughs have been made in immunotherapy. The present study established that tumor cells on ENKTL have a high expression of programmed death receptor ligand (PD-L1) associated with poor prognosis[1,2]. PD-1/PD-L1 drugs have been used in clinical trials to treat relapsed/refractory ENKTL. Kwong et al[3] used the PD-1 inhibitor pembrolizumab to treat 7 patients with relapsed refractory NK/T-cell lymphoma. Complete remission was achieved in 5 patients and partial remission in 2 patients. Additionally, the ORR of all patients was 100%.

Treatment with pembrolizumab provides a new effective salvage treatment program for patients with relapsed and refractory diseases. The 2018 NCCN guidelines[4] incorporated pembrolizumab into the NK/T-cell lymphoma rescue treatment regimen.

Generally, PD-1 inhibitors are safe for use. Their common adverse reactions include fatigue, fever, chills, infusion reactions, and organ-specific

immune reactions such as rash, enteritis, pneumonia, hepatitis, nephritis, myocarditis, and others[4-6]. Most of these adverse reactions have been graded 1-2, but nearly 10% of patients have serious side effects or even life-threatening grade 3-to-4 immune abnormalities. The guidelines recommend permanent discontinuation of PD-1 inhibitor treatment in the presence of grade 3-4 adverse reactions[7].

In the present case study, the patients' renal function significantly declined following the infusion of PD-1 inhibitors, with the estimated glomerular filtration rate (eGFR) decreasing from 82.48 ml/min/1.73 m^2 to 26.06 ml/min/1.73 m^2. PD-1 inhibitor-related renal impairment was defined by elevated serum creatinine/acute renal failure, characterized by azotemia, elevated creatinine, inability to maintain acid-base or electrolyte balance, and changes in urine output. Thus, the patient was identified to suffer moderate (G2) renal damage, indicated by creatinine levels 2-3 times higher than the baseline level. According to previous studies, the most common type of renal damage associated with PD-1 inhibitors is acute interstitial nephritis. Its clinical and pathological manifestations include acute adrenal insufficiency and renal tubulointerstitial nephritis (interstitial pleomorphic inflammatory infiltration dominated by CD3+ and CD4+ T cells), respectively[8].

Cortazar et al[9] analyzed published clinical trials of patients with immune therapy and found an overall rate of 2.2% of acute kidney injury (AKI) among 3,695 patients and a 0.6% incidence of grade III or IV AKI requiring dialysis. Preliminary studies[9] have indicated a low incidence rate of AKI (2-3%) after immune therapy, with acute interstitial nephritis (AIN) as the most common biopsy result for AKI. Phase I and phase II trials have also revealed that the incidence rate of AKI as nephritis was 6.7%. In addition, some cases showed that the time range of biopsy diagnosis of AIN was 1 to 12 months[9,10].

The 2019 management guidelines for NCCN[12] immunotherapy-related toxicity outlined that immunotherapy must be suspended following grade 1-2 renal injury development. Only after alleviating kidney injury to grade 1 and stabilizing creatinine levels immunotherapy can be restarted with simultaneous steroid administration. In cases of severe proteinuria (grade 3-4), immunotherapy must be permanently discontinued. Most cases respond to steroids in the early stages of kidney injury, with few patients requiring dialysis.

IgA nephropathy is a rare side effect of immunotherapy with few publications on PubMed. Tanabe et al[11] reported a patient with advanced gastric cancer who developed IgA nephropathy following nivolumab treatment. The patient developed proteinuria and microhematuria two months after the initiation of treatment, and renal dysfunction progressed until IgA nephropathy was confirmed by biopsy at 8 months. This case report is consistent with Kishi et al[12] and Oki et al[13].

Previous cases have revealed that abnormal urinalysis and biopsy diagnosis of IgA nephropathy was conducted a few months after the first use of immune checkpoint inhibitors. In addition, Belliere et al[8] reported 9 cases of immune checkpoint inhibitor-related renal disorders. However, in most cases, acute kidney injury occurred at 4-12 weeks after the initiation of treatment with characteristic tubulointerstitial nephritis. Still, renal biopsy was started after two months.

In the present case, the patient had elevated body temperature, elevated serum creatinine, and a decreased estimated glomerular filtration rate within 24 hours (Figure 1c). Moreover, the patient had proteinuria and microhematuria before the first administration of the drug, contrary to previous case reports. This led to suspicions that IgA nephropathy diagnosed by biopsy may be an existing disease and not due to the treatment. Besides, the reuse of PD-1 inhibitors following the recovery of renal function did not lead to the recurrence of abnormal renal function. This contradicts previous cases where the continued use of immune checkpoint inhibitors often led to renal function deterioration. Based on these differences, we affirmed that the patient's IgA nephropathy was an existing condition not related to the use of PD-1 inhibitors.

Based on the literature, patients with renal injury following treatment with PD-1 inhibitors should be treated in time to improve renal function to enable continued anti-PD-1 therapy. Our study suggests that clinicians should always establish whether a patient's kidney injury is related to anti-PD-1 treatment and develop an effective follow-up treatment plan, as recovering renal function is crucial to patients.

Conclusions

With the widespread use of immunotherapy, more attention should be given to managing its side effects. The toxicity and side effects associated with immunotherapy are often non-specific;

hence it is crucial to determine the relationship between immunotherapy and its side effects to treat patients effectively. For example, our patient developed grade 3 renal injury after using a PD-1 inhibitor. Additional examination revealed that renal insufficiency was unlikely due to immunotherapy, thus avoiding unnecessary drug discontinuation.

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Authors' Contributions
JH conceived the case idea. TST, XF collected the data, organized it, and presented it in figures. HY and XXX developed the first manuscript draft. All the authors read and approved the final draft of the manuscript.

Conflict of Interests
The authors declare no competing interests.

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