Case Report

Rapidly Progressive Acute Kidney Injury Associated with Nivolumab Treatment

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Keywords

Immune checkpoint inhibitors · Nivolumab · Acute kidney injury · Acute tubular necrosis · Renal biopsy

Abstract

A 63-year-old man with pulmonary adenocarcinoma was treated with nivolumab. High fever developed within several hours after the first administration of nivolumab; subsequently, serum creatinine levels kept increasing daily. We diagnosed acute kidney injury (AKI) as an immune-related adverse event; the patient was initially treated with 50 mg prednisolone, and the dose was then tapered. Renal biopsy pathologically revealed tubulointerstitial inflammation with strong infiltration of only T cells that were CD3⁺, CD4⁺, and CD8⁺. The infiltration of CD163⁺ M2 macrophage was also observed. AKI within 1 week after the administration of nivolumab seems to be rare; therefore, the present case provides important findings useful in daily clinical practice.

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Published by S. Karger AG, Basel

Introduction

Immune checkpoint inhibitors (ICIs) have recently emerged as a frontline treatment for an increasing number of non-small cell lung cancers (NSCLCs), because of their long-term tumor control and extended patient survival. Programmed cell death-1 (PD-1) antibodies including

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Fig. 1. Clinical course after the first dose of nivolumab. High fever occurred immediately after the administration of nivolumab, and the patient's serum creatinine level rapidly increased within several days. Corticosteroid therapy was effective for treating renal failure. The high fever resolved, and serum creatinine levels improved remarkably.

nivolumab have antitumor activity as they target PD-1 or programmed cell death ligand 1 (PD-L1). Various immune-related adverse events (irAEs) have been also reported [1]. However, the incidence of renal adverse effects induced by ICIs was relatively low in previous randomized clinical trials [2, 3]. Furthermore, there has been no report concerning rapid progressive acute kidney injury (AKI) within several days. Therefore, herein, we describe a case of rapidly progressive severe AKI associated with nivolumab treatment for locally advanced NSCLC.

Case Report

A 63-year-old man with a locally advanced pulmonary adenocarcinoma without any oncogenic driver mutation (cT3N2M0, stage IIIB) received combination chemotherapy of docetaxel and cisplatin with concomitant thoracic irradiation [4] in May 2018. After receiving the first cycle of chemotherapy, he developed an abscess in contact with the primary lesion in the right upper lobe. Therefore, we were compelled to discontinue chemoradiotherapy owing to the need for antibiotic therapy for the pulmonary abscess (tazobactam/piperacillin 4.5 g, 3 times/day). Although the results of the blood culture were negative, we changed the regimen to amoxicillin hydrate and potassium clavulanate as part of “de-escalation” (switching to or interrupting a drug class resulting in a narrow spectrum of coverage) and continued this treatment for 6 weeks [5]. We were concerned about the exacerbation of the pulmonary

Fig. 2. Hematoxylin and eosin stain (**a**, **b**), and periodic acid methenamine silver stain (**c**). Pathological findings of the biopsied specimen obtained from the left kidney showed acute tubulointerstitial nephritis. Severe tubulointerstitial inflammation, tubular atrophy, and an area of interstitial edema with mononuclear cells and eosinophils were observed.

abscess if we were to retry treatment with cisplatin and docetaxel. Because PD-L1 was expressed in more than 50% of the cancer cells in the specimen obtained via bronchoscopy (the tumor proportion score was approximately 95%), we selected nivolumab as second-line chemotherapy. Therefore, our patient received 170 mg (3 mg/kg) nivolumab intravenously in June 2018.

However, the patient experienced shaking chills and developed high fever within several hours after the administration of nivolumab, suggesting the manifestation of an infusion reaction. The patient's body temperature was nearly 40°C, blood pressure (BP) was 140/76 mm Hg, heart rate (HR) was 60 bpm, and blood oxygen saturation (SpO₂) was 96% without oxygen inhalation; no anaphylactic reactions were observed. The patient was treated with acetaminophen-containing tablets, but his fever persisted over a period of time. On day 4 after receiving the first dose of nivolumab, his serum creatinine level was elevated (4.61 mg/dL) and was increasing everyday (Fig. 1).

AKI was suspected to be induced by nivolumab, and the patient was treated with 50 mg prednisolone on day 5 on the suggestion of a nephrologist. Immediately after the administration of prednisolone, his serum creatinine level gradually started decreasing. The dose of prednisolone was tapered by 10 mg per week (Fig. 1).

On day 8 of nivolumab treatment (3 days after the start of prednisolone), we performed a renal biopsy. The pathological examination of the biopsy specimen obtained from the left kidney showed acute tubulointerstitial nephritis (Fig. 2). Severe tubulointerstitial inflammation, tubular atrophy, and an area of interstitial edema with mononuclear cells and eosinophils were observed. Immunohistochemical staining showed the infiltration of CD3⁺ T cells, CD4⁺ helper T cells, and CD8⁺ cytotoxic T cells without CD20⁺ B cell infiltration (Fig. 3). The infiltration of CD68⁺ and CD163⁺ macrophage was also observed. The drug-induced lymphocyte stimulation test (DLST) result was negative for nivolumab, rabeprazole, and amoxicillin.

After discharge in August 2018, computed tomography scans of the chest showed remarkable tumor shrinkage (Fig. 4).

Discussion

We encountered a case of AKI induced by nivolumab for the treatment of advanced NSCLC. While many cases have shown various irAEs associated with ICIs, AKI is relatively rare. Cortazar et al. [6] analyzed and reported data from published phase 2 and 3 clinical

Fig. 3. Immunohistochemical staining showed the infiltration of CD3⁺ T cells, CD4⁺ helper T cells, and CD8⁺ cytotoxic T cells without CD20⁺ B cell infiltration. The infiltration of CD68⁺ and CD163⁺ macrophage was also observed. Only T cell response and macrophage growth were microscopically evident on immunostaining.

Fig. 4. Computed tomography scan of the chest before treatment with nivolumab showed a mass in the right upper lobe of the lung (a). The tumor shrunk with cavity formation and maintained regressing on day 45 after the first dose of nivolumab (b).

trials of patients with adverse renal outcomes and found the overall incidence of AKI to be 2.2% among a total of 3,695 patients. AKI occurred in patients who received monotherapy using ipilimumab (2.0%), nivolumab (1.9%), or pembrolizumab (1.4%) [6]. However, an increasing number of cases of AKI have been reported due to its recent widespread availability for various malignancies. For example, severe acute interstitial nephritis has been reported after two doses of combination ICIs including nivolumab and ipilimumab for metastatic melanoma [7]. In addition, acute tubulointerstitial nephritis (ATIN) has been reported [8, 9]. In these cases, the symptoms have been reported to occur 6–12 weeks after the initial dose of ICIs; while in the present case, rapid progression of renal dysfunction was observed

within several days. To the best of our knowledge, AKI within 1 week after the administration of nivolumab is rare; therefore, our case provides important findings useful in daily clinical practice.

The pathological findings of specimen obtained by renal biopsy showed severe ATIN with marked infiltration of CD3⁺ T cells, CD4⁺ T cells, and CD8⁺ T cells, which is consistent with the summary of previous reports concerning tubulointerstitial infiltrating cells in ICI-induced ATIN described by Tabei et al. [10]. These findings suggest that T cells play important roles in establishing ATIN by ICIs. The infiltration of CD163⁺ M2 macrophage was also observed in the present case. M2 macrophages are considered to tune the inflammatory response, thereby promoting tissue remodeling or repair and sometimes driving the fibrotic response during tissue injury [10]. In the present case, CD163⁺ M2 macrophages seemed to be induced by corticosteroid administration.

The pathogenesis of ICI-induced kidney injury is unknown. However, several potential hypothetical explanations have recently been described. Cortazar et al. [11] discussed two main hypotheses of renal failure induced by ICI. One is breakdown of immune tolerance due to endogenous antigens, and the other is breakdown of immune tolerance due to combination drugs. The latter hypothesis is based on a previous report that 14 out of 19 ATIN patients, while using ICIs, combined suspected drugs such as proton pump inhibitor (PPI) and NSAIDs for drug-induced interstitial nephritis [11]. Similarly, Perazella et al. [12] reviewed nephrotoxicity in cancer immunotherapies and discussed the mechanisms underlying ICI-induced kidney injury. Among them, we consider two hypotheses for the pathogenesis of AKI in the present case.

Firstly, the formation of new or reactivated T cells against tumor antigens may cross-react with off-target kidney tissues. The loss of peripheral tolerance of autoreactive T cells against tubular cells is hypothesized as an underlying mechanism of ICI-induced tubulointerstitial nephritis. In addition, certain tissues may normally express checkpoint receptors that then bind to anti-ICI antibodies, triggering an immune reaction against that tissue. PD-L1 is expressed on renal tubular epithelial cells [13]. In the present case, the SP263 assay, one of the PD-L1 immunohistochemistry assays, exhibited PD-L1 positivity of some cells on the epithelial cell membrane of the tubule (data not shown). The results of the PD-L1 immunohistochemistry assays are consistent with previous studies and support the mechanism for drug-induced nephropathy.

Secondly, the reactivation of drug-specific T cells through ICI-induced loss of tolerance seems to be another mechanism of ICI-induced ATIN [14]. In two published series, many of the patients had concomitant administration of drugs known to cause ATIN (nonsteroidal anti-inflammatory drugs, PPI, etc). In a previous case, lansoprazole contributed to the development of ATIN during nivolumab therapy. The authors of that case also described the importance of recognizing concomitant medications causing AKI associated with PD-1 blockade by ICIs. In that case, the blockade of the intrinsic PD-1 signaling pathway by anti-PD-1 therapy possibly disrupted the patients' long-standing immunological tolerance against lansoprazole by modulating T-cell immunoreactivity [15]. Therefore, we should also consider the possibility of PPI-induced AKI triggered by nivolumab in our patient. In contrast, our case had been treated with antibiotics including penicillin known to be causal drugs for ATIN. PPI and/or antibiotics might have caused ATIN in the present case. We should give scrupulous attention to nivolumab treatment in case with co-administered PPI and antibiotics.

In conclusion, we report a rare case of nivolumab-induced ATIN. To our knowledge, this is the first report of a rapid irAE affecting renal function. There are a few reports about irAEs of AKI, and further investigations are needed to determine the mechanism of how ICIs affect the kidneys. Nevertheless, if irAEs occur, prompt treatment is needed to prevent patient death.

Statement of Ethics

Ethical approval for the publication of his case was obtained from the patient.

Disclosure Statement

Research funding was allocated to Keiichi Fujiwara by Hisamitsu Pharmaceutical Co., Inc.

Funding Sources

We declare that the authors received no funds for this research.

Author Contributions

All authors contributed to this manuscript and approved the final manuscript.

References

- 1 Hryniewicki AT, Wang C, Shatsky RA, Coyne CJ. Management of immune checkpoint inhibitor toxicities: a review and clinical guideline for emergency physicians. *J Emerg Med*. 2018;55:489–502.
- 2 Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–35.
- 3 Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018–28.
- 4 Segawa Y, Kiura K, Takigawa N, Kamei H, Harita S, Hiraki S, et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. *J Clin Oncol*. 2010 ;28:3299–306.
- 5 Marra A, Hillejan L, Ukena D. [Management of lung abscess]. *Zentralbl Chir*. 2015;140:S47–53.
- 6 Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int*. 2016;90:638.
- 7 Murakami N, Borges TJ, Yamashita M, Riella LV. Erratum: severe acute interstitial nephritis after combination immune-checkpoint inhibitor therapy for metastatic melanoma. *Clin Kidney J*. 2016;9:649.
- 8 Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol*. 2006;24:2283–9.
- 9 Fadel F, El Karoui K, Knebelmann B. Anti-CTLA4 antibody-induced lupus nephritis. *N Engl J Med*. 2009;361:211–2.
- 10 Tabei A, Watanabe M, Ikeuchi H, Nakasatomi M, Sakairi T, Kaneko Y, et al. The analysis of renal infiltrating cells in acute tubulointerstitial nephritis induced by anti-PD-1 antibodies: a case report and review of the literature. *Intern Med*. 2018;57(21):3135–9.
- 11 Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int*. 2016;90:638.
- 12 Perazella MA, Shirali AC. Nephrotoxicity of cancer immunotherapies: past, present and future. *J Am Soc Nephrol*. 2018;29(8):2039–52.
- 13 Ding H, Wu X, Gao W. PD-L1 is expressed by human renal tubular epithelial cells and suppresses T cell cytokine synthesis. *Clin Immunol*. 2005;115(2):184–91.
- 14 Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int*. 2016;90(3):638–47.
- 15 Koda R, Watanabe H, Tsuchida M, Iino N, Suzuki K, Hasegawa G, et al. Immune checkpoint inhibitor (nivolumab)-associated kidney injury and the importance of recognizing concomitant medications known to cause acute tubulointerstitial nephritis: a case report. *BMC Nephrol*. 2018;19(48):2018.