Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2021;11:270–274
DOI: 10.1159/000517502
Received: January 26, 2021
Accepted: May 29, 2021
Published online: September 9, 2021

Single Case

Development of Nivolumab/Ipilimumab-Associated Autoimmune Nephritis during Steroid Therapy

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Keywords
Autoimmune nephritis · Checkpoint inhibitor toxicity · Acute interstitial nephritis · Acute kidney injury · Nivolumab

Abstract
Immunotherapy using immune checkpoint inhibitors revolutionized therapies for a variety of malignancies. Nivolumab, an antibody blocking programmed cell death 1 protein, and ipilimumab that blocks cytotoxic T-lymphocyte-associated protein 4 effectively target tumor cells by disinhibiting the endogenous immune response. At the same time, unrestrained T-cell activation may trigger a range of immune-mediated side effects including kidney injury. Steroid therapy constitutes the mainstay of treatment of these adverse events, but dosage, route of administration, and approach to nivolumab re-exposure remain unclear. Here, we report the case of a 72-year-old male patient who developed severe nivolumab/ipilimumab-associated acute kidney injury while on oral steroid therapy for immune-mediated colitis. Acute interstitial nephritis was confirmed by renal biopsy. Administration of high-dose intravenous steroid doses was required to revert declining renal function.

Introduction

Immune checkpoint inhibitors (ICPIs) have been implemented as an important therapeutic principle in various oncological therapy protocols. The checkpoint inhibitors nivolumab and ipilimumab are monoclonal antibodies that block programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), respectively. The

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targets are inhibitory receptors expressed on T cells. Administration of nivolumab/ipilimumab elicits an immune response against malignant cells that no longer may evade detection and destruction by the immune system. ICPIs are commonly included in regimes for malignant melanoma, nonsmall-cell lung cancer, or kidney cancer and other malignancies. While the therapeutic efficacy of these novel immune therapies is most impressive, they are at the same time burdened with a variety of immune-related adverse events (IRAEs). IRAEs can affect a wide range of organs. IRAEs most frequently observed with ICPIs are rash, colitis, hepatitis, and hypophysitis [1]. The incidence of AKI in treatment with nivolumab is rather low, at levels of 2.2% [2]. AKI is graded into different groups, grade 3 being defined by an increase of serum creatinine (SCr) levels >3-fold above baseline or SCr >4.0 mg/dL [2]. Grade 4 is defined by life-threatening consequences that require dialysis. The incidence of grade 3 or 4 AKI under ICPI has been reported to occur in 0.6% of cases [3]. In comparison with nivolumab monotherapy, AKI may become more than twice as frequent when nivolumab is combined with ipilimumab [3]. Herein, we present the case of a patient that developed AKI due to nivolumab/ipilimumab therapy in spite of oral steroid therapy and required excessive intravenous doses for recovery of renal function.

Case Report

A 72-year-old male patient presented as an outpatient for a routine checkup and was admitted due to acute kidney failure. He had been diagnosed with ulcerate nodular melanoma 10 months earlier. His further medical history included atrial fibrillation and prostatic hyperplasia. At the time of admission, his medication consisted of methylprednisolone (16 mg daily), bisoprolol, and pantoprazole. In June 2020, he had received double immunotherapy with nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg). Fourteen days later, the patient was admitted with high fever (39°C) that was accompanied by mild prerenal AKI or hemoconcentration (fractional sodium excretion <0.1%, otherwise normal urinalysis, and SCr max 1.4 mg/dL). Renal function recovered within 4 days (SCr 1.1 mg/dL) upon volume expansion (Fig. 1) before steroid exposure. Three days later, the patient developed grade 3 autoimmune colitis. In accordance with the recommendations of the "American Society of Clinical Oncology (ASCO)," steroid therapy was initiated at 1 mg/kg/day methylprednisolone for the colitis, which was tapered over 5 weeks [2]. After clinical stabilization, the therapy was resumed with a single dose of 480 mg nivolumab. The asymptomatic patient presented for a routine follow-up after 2 weeks. As SCr had drastically increased from 1.01 mg/dL to 4.93 mg/dL, he was immediately admitted to the hospital. Mildly elevated urinary protein excretion (protein to creatinine ratio 0.22 mg/mg) as well as mild hematuria was observed. The urinary sediment revealed sparse leukocyturia without cylinders or signs of acute tubular necrosis, while fractional excretion of sodium now indicated renal AKI (4.4%). In face of the rapid and unexplained AKI, a percutaneous renal biopsy was performed that revealed a severe, acute, and partly granulomatous tubule-interstitial nephritis with signs of a parenchyma destruction, while there were no signs of glomerular damage (shown in Fig. 2A–C). A CD3-positive T-cell infiltrate was found interstitially. CD4-positive cells predominated over CD8-positive cells, being accompanied by sparse B lymphocytes (shown in Fig. 2D–F). We escalated steroid therapy to 250 mg methylprednisolone intravenously over 2 days. However, kidney function continued to decline, with an SCr of 5.7 mg/dL. A significant improvement in kidney function was only achieved after further escalation to 500 mg intravenous methylprednisolone for 1 day. The steroid therapy was switched to oral prednisone, and

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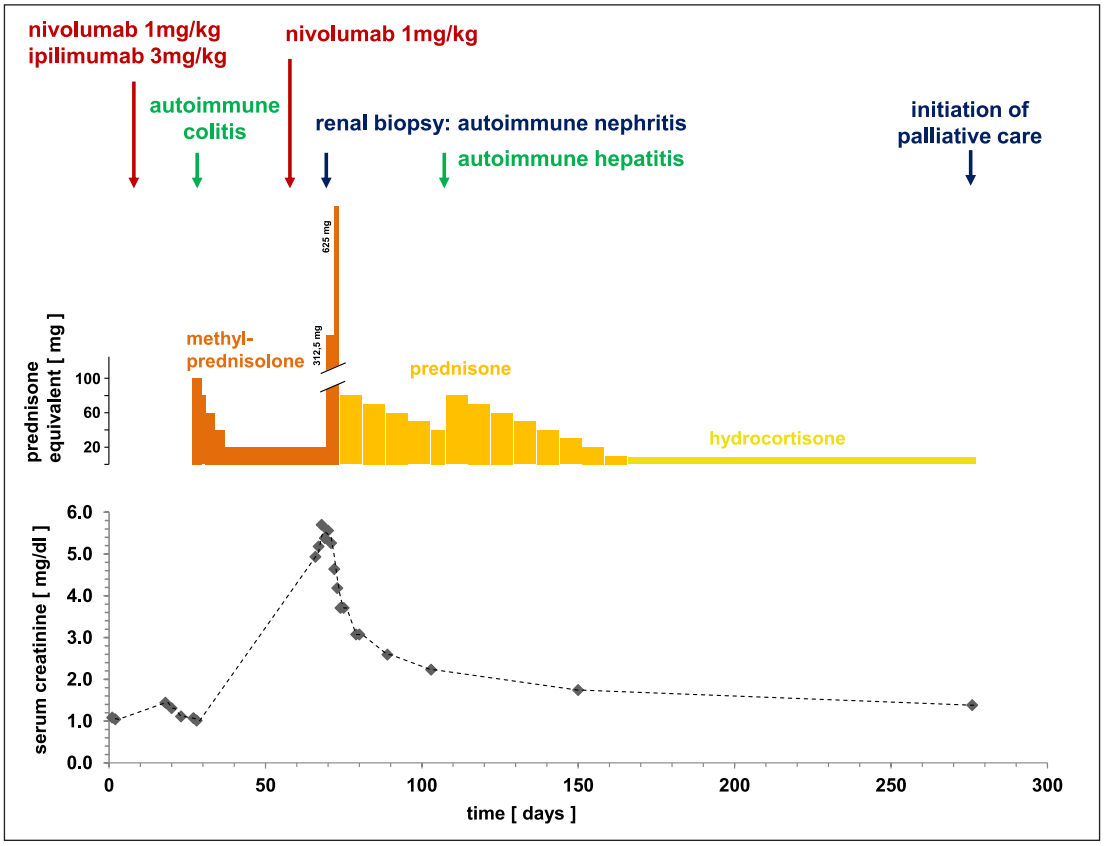

Fig. 1. Time course of renal function and steroid therapy. Graph indicates serum creatinine in relation to steroid dose (stated as prednisone equivalent dose for each steroid), immune therapy, and other significant clinical events.

treatment with nivolumab/ipilimumab was discontinued. In a follow-up visit 5 weeks after discharge, a gradual decline of the SCr to 2.23 mg/dL was recorded. Over the course of 3 months under steroids, a continuous decline of SCr levels to 1.74 mg/dL was noted. After 5 weeks during steroid tapering to 40 mg/day, an acute elevation of alanine transaminase (AST) to 474 U/L was observed, suggesting grade 3 autoimmune hepatitis. AST rapidly fell to 83 U/L upon transient steroid escalation to 80 mg. Steroid tapering was resumed and the regime switched to hydrocortisone for this purpose. However, a dose of 30 mg hydrocortisone was maintained. Seven months after the renal biopsy, the patient was readmitted due to progressive disease with disseminated metastatic spread, and therapy was limited to palliative care. In contrast, a decrease of SCr to 1.38 mg/dL indicated further recovery of renal function.

Discussion

AKI occurs more frequently with dual checkpoint inhibitor therapy (CTLA-4 blocking antibody + PD-1 inhibitor) [3]. Delayed onset of AKI that follows other IRAEs such as colitis is frequently observed [4]. We report a case of a patient who developed a grade 3 AKI and further a grade 3 autoimmune hepatitis under dual checkpoint inhibitor therapy despite receiving oral steroids according to current guidelines. Several reports of acute interstitial

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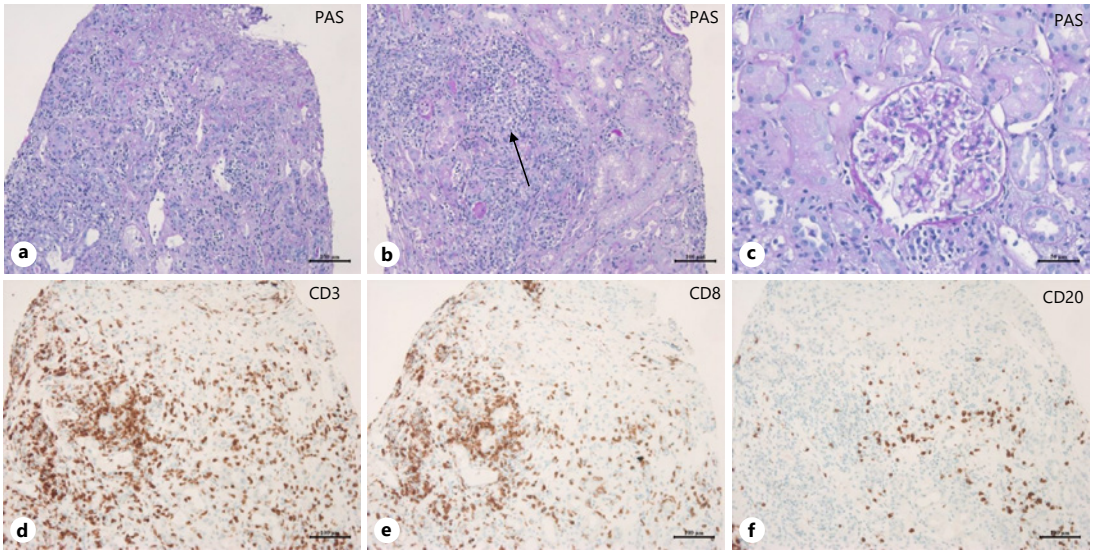

Fig. 2. Renal biopsy. PAS staining of the patient's renal biopsy reveals tubulointerstitial nephritis (**A**), with concomitant granulomatous inflammation (**B**) and absence of glomerular damage (**C**). Magnification, ×20 (**C**). CD3 staining shows the inflammatory infiltrate is dominated by CD3-positive T lymphocytes (**D**), while a significant proportion of CD8-positive cytotoxic T lymphocytes is observed (**E**). A limited number of B lymphocytes are indicated by CD20 staining. Magnification, ×10 throughout the figure unless otherwise indicated. PAS, periodic acid-Schiff.

nephritis (AIN) under nivolumab therapy have been published [3, 5–7]. However, to our knowledge, this is the first report of AIN developing despite ongoing steroid therapy. Autoimmune renal disease thus should not be ruled out due to current steroid therapy. Close monitoring of renal function is required, as standard steroid dosages may fail to prevent occurrence of AIN.

Optimal steroid dosage and route of administration to treat ICPI-associated AKI have not been tested in controlled trials and remain unclear. Drastic doses of intravenous steroids that well exceeded current guidelines by the American Society of Clinical Oncology (ASCO) were needed to revert a progressive decline of kidney function in our patient. Dual checkpoint inhibitor therapy may predispose to a failure of steroid therapy at regular dosage, and patients need close surveillance during therapy. Clinicians should consider dose escalation particularly in refractory cases. Short-term escalation of steroids may seem preferable to switching to another class of immunosuppressant such as infliximab [8, 9] unless indicated by extrarenal IRAE. In conclusion, our case shows that ICPI-associated AKI may occur despite ongoing oral steroid therapy and dose escalation needs to be considered for refractory cases.

Statement of Ethics

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. This article does not contain any studies with human participants or animals performed by any of the authors. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The report is solely based on information obtained during patient care without any interventions. Thus, it is exempt from ethics committee approval.

Conflict of Interest Statement

The authors have declared that there are no conflicts of interest.

Funding Sources

No funding was received for this study.

Author Contributions

E.G., W.B.W., and T.H. analyzed and interpreted patient data; C.S. and M.E. analyzed the renal biopsy and prepared the histopathological figure. E.G., T.H., and W.B.W. drafted the manuscript. T.H. and G.W. revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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