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Acute interstitial nephritis with immunotherapy; a growing entity?

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ABSTRACT

We report a case of acute kidney injury (AKI) secondary to immune-mediated acute interstitial nephritis (AIN), with supporting diagnostic results and a successful response to treatment. This entity is gaining increasing recognition with the burgeoning use of immunotherapy agents in oncology. The timeline for the development of AIN from the initiation of immunotherapy varies, and may range in severity from asymptomatic to severe, organ-threatening and with life threatening consequences. Renal biopsy should be performed to confirm the diagnosis due to the potential impact of discontinuation of immunotherapy on cancer survival. Re-challenge with immunotherapy is reasonable once renal function recovers.

Case Report

Implication for health policy/practice/research/medical education:
Immune-mediated acute interstitial nephritis is the most commonly reported etiology for acute kidney injury related to immune checkpoint inhibitors.

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Introduction

Checkpoint inhibitors have burgeoned in use in the treatment of solid organ malignancies since ipilimumab, a cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitor, was approved by the FDA in 2011 for treatment of melanoma and showed dramatic improvements in progression free survival - and even an absence of disease after 10 years in more than 20% of patients with metastatic melanoma who received a single round of treatment (1). Checkpoint inhibitor use is now a cornerstone of treatment in a range of solid organ malignancies and even earned the 2018 Nobel Prize for Medicine. However recognised immune-related adverse events (irAEs) are common including hypophysitis, dermatitis, hepatitis and colitis (2). However nephritis seems a rare complication, and as such treatment decisions are hampered by a lack of evidence. Here we describe a case of acute interstitial nephritis (AIN) caused by Nivolumab, a programmed cell death protein 1 (PD-1) inhibitor antibody – and its subsequent successful management.

Case Presentation

A 71-year-old male was admitted for investigation of an asymptomatic acute kidney injury (AKI) noted on routine blood tests. He had a background of metastatic squamous cell carcinoma from the left lower lobe of the lung, and was receiving Nivolumab, a fully humanised immunoglobulin G4 PD-1 immune checkpoint inhibitor antibody, fortnightly 3 mg/kg from 5 months previously with no noted derangements in renal function last checked 16 days prior to admission. Other medical history included type 2 diabetes mellitus managed on oral hypoglycemics and chronic obstructive pulmonary disease.

On admission, his serum creatinine was markedly elevated at 339 umol/L (Figure 1) (reference range 60-110 umol/L). He had been otherwise asymptomatic with no inter-current illness, gastrointestinal symptoms, medication changes including known nephrotoxins such as non-steroidal anti-inflammatory medication or anti-hypertensive initiation – or other relevant causative exposures. The only other admission medication included

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metformin, vildagliptin, and as required salbutamol – all of which were present for longer than 3 years.

Following admission, his mid-stream urine showed no red or squamous cells, though had between 10-50 $\times 10^6$/L white cells with white cell casts but no urinary eosinophils, as well as urinary glucose and protein. There were no nitrites, ketones, urobilinogen or bilirubin and urinary pH was 5. The protein to creatinine ratio was elevated at 40 mg/mmol (reference range <11 mg/mmol), and albumin to creatinine ratio 7.4 mg/mmol (reference range <2.5 mg/mmol). Computerized tomography showed no urinary obstruction but mild bilateral perirenal stranding, and investigation into other putative causes was negative (including viral hepatitis serology, anti-nuclear, anti-neutrophil cytoplasmic and anti-glomerular basement membrane antibodies, an extractable nuclear antigen panel, complement, immunoglobulin and paraprotein investigation). A diagnosis of tubular dysfunction was further supported by a serum hyperkalemia of 7.2 mmol/L (reference range 3.5-5.2 mmol/L). Due to the severity and clinical diagnosis of AIN, intravenous methylprednisolone was commenced on admission (day 0) at a dose of 500 mg daily for 3 days followed by oral prednisolone (1 mg/kg) leading to an improvement in renal function. Due to the potential impact of stopping nivolumab with his metastatic cancer, a confirmatory renal biopsy was undertaken day 6 of admission which confirmed partially treated AIN (Figure 2). The patient was discharged on a weaning schedule of prednisolone, with ongoing improvement of his renal function on follow up.

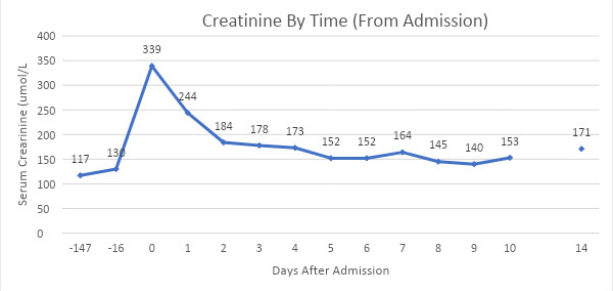

Figure 1. Serum creatinine from admission. Methylprednisolone started day 0.

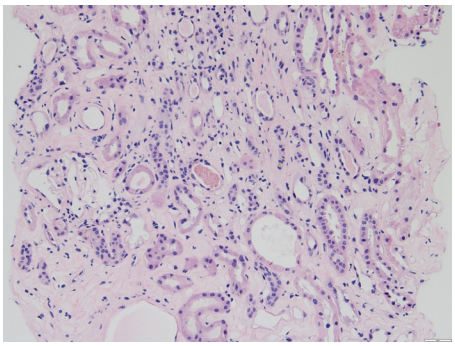

Figure 2. Renal biopsy; hematoxylin and eosin stain showing interstitial lymphocytes and tubular dilatation.

Discussion

Immune checkpoint inhibitors (CPIs) are have revolutionised the landscape of solid organ tumour management, and as such have burgeoned in use. Anti-tumour T checkpoint inhibitor antibodies such as anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed death 1 (PD-1) have shown significant clinical benefits in tumour regression and cancer survival. In Australia, the Therapeutic Goods Administration (TGA) of approved indications for Nivolumab include melanoma, non-small cell lung cancer (NSCLC), clear cell renal cell carcinoma, classical Hodgkin lymphoma (cHL), squamous cell cancer of the head and neck and urothelial carcinoma (3).

However immune-related toxicities are common and increasingly recognized with CPI therapy (4). Immune-mediated nephrotoxicity though rare, is also an important complication of CPIs (4). The mechanism underlying CPI induced kidney injury is unknown, but there are some possible explanations based of non-renal irAEs. AIN is the most commonly reported etiology for AKI related to CPI (5), though cases of glomerulopathies have also been reported in the literature to be associated with CPI use (5).

The timeline for CPI-mediated AIN seems more variable than traditional drug-induced AIN, often developing long after the first or last dose of drug (6). Immunotherapy-related AIN could be due to the loss of tolerance of drug specific effector T cells with the inhibition of PD-1 signaling. It is also important to recognize that CPIs can alter the long-lasting immunological tolerance against other concomitant medications well-known to cause AIN during the assessment of AKI associated with CPI. The mainstay of diagnosis is a renal biopsy, which should be performed when immune-mediated nephrotoxicity is suspected. However drug-induced lymphocyte stimulation test (DLST) for suspected culprit drug may also be useful in some circumstances (7).

Though AKI is an uncommon complication of checkpoint inhibitor immunotherapy [under 1% in one study of single agent immunotherapy (8)], it is likely under-recognized and under-diagnosed and the widespread and increasing use of immunotherapy means it is likely to have an increasing prominence. Furthermore certain combinations may portend a higher risk of renal related complications (9). In one retrospective case series of 13 patients with CPI-related, AIN was histologically diagnosed in 12 with 4 patients requiring haemodialysis.

After evaluation of all potential causes of AKI, discontinuation of CPI and a course of corticosteroids should be considered. Severity is often graded by the American Society of Clinical Oncology (ASCO)

guidelines from 1 to 4 based on the change in serum creatinine and consequences (10). ASCO and the Australian Public Assessment Report (AusPAR) of TGA recommends permanent discontinuation of CPI treatment for severe nephritis, however re-challenging with CPI may be reasonable for cases with mild to moderate renal dysfunction when serum creatinine returns to baseline and corticosteroid treatment is complete (3).

Though steroids in AIN in general is controversial, and often reserved for severe cases (4), since there is a paucity of evidence for CPI related AIN to guide treatment decisions. Case reports have described improvement with prednisone 1 mg/kg tapered over a period of 1–2 months, while serum creatinine is closely monitored (4).

Conclusion

In summary, AIN related to CPI is an increasingly recognized entity. Here we report a biopsy-proven case, and its subsequent treatment with marked improvement of renal function.

Authors' contribution

Guarantor of the article: John Chetwood. JDC and LM and wrote the manuscript and provided the literature background. HL, MP and JH provided support and advice on the manuscript composition .All authors approved the final version of the manuscript.

Conflicts of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Informed consent was obtained from the patient for publication of the report.

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