Acute Tubulointerstitial Nephritis in a Patient on Anti-Programmed Death-Ligand 1 Triggered by COVID-19: A Case Report

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Abstract
Rationale: Immune checkpoint inhibitors are monoclonal antibodies used in the treatment of various types of cancers. The downside of using such molecules is the potential risk of developing immune-related adverse events. Factors that trigger these autoimmune side effects are yet to be elucidated. Although any organ can potentially be affected, kidney involvement is usually rare. In this case report, we describe the first known instance of a patient being treated with an inhibitor of programmed death-ligand 1 (anti-PD-L1, a checkpoint inhibitor) who develops acute tubulointerstitial nephritis after contracting the severe acute respiratory syndrome coronavirus 2.

Presenting concerns of the patient: A 62-year-old patient, on immunotherapy treatment for stage 4 squamous cell carcinoma, presents to the emergency department with symptoms of lower respiratory tract infection. Severe acute kidney injury is discovered with electrolyte imbalances requiring urgent dialysis initiation. Further testing reveals that the patient has contracted the severe acute respiratory syndrome coronavirus 2.

Diagnosis: A kidney biopsy was performed and was compatible with acute tubulointerstitial nephritis.

Interventions: The patient was treated with high dose corticosteroid therapy followed by progressive tapering.

Outcomes: Rapid and sustained normalization of kidney function was achieved after completion of the steroid course.

Novel findings: We hypothesize that the viral infection along with checkpoint inhibitor use has created a proinflammatory environment which led to a loss of self-tolerance to renal parenchyma. Viruses may play a more important role in the pathogenesis of autoimmunity in this patient population than was previously thought.

Keywords
nephritis, COVID, immunotherapy, anti-PD-L1, checkpoint inhibitor

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Introduction
Over the last decade, immune checkpoint inhibitors (ICI) have created exciting new therapeutic options for cancer treatment. Unfortunately, stimulating the immune system to fight malignancy comes with the potential risk of developing various immune-related adverse events (irAE). One of the most frequently encountered irAE that pertains to the kidney is acute tubulointerstitial nephritis (ATIN). While the specific pathophysiology remains obscure, proposed mechanisms include auto-immune hypersensitivity reactions, ultimately leading to parenchymal inflammation with consequent decline in kidney function.
Viruses are a known cause of ATIN as well as other autoimmune diseases. However, whether they are implicated in triggering irAE is still uncertain. A potential link has been recently discovered between Epstein-Barr virus and autoimmune encephalitis in a patient on immunotherapy. Here, we describe the first clear temporal association between coronavirus disease 2019 (COVID-19) and the development of ATIN in the context of immunotherapy.

A 62-year-old female, known for poorly differentiated squamous cell carcinoma of unknown primary origin with lymph node metastases and peritoneal carcinomatosis, had been undergoing investigational treatment with durvalumab (1500 mg monthly) since May of 2017. In September of 2019, she developed a generalized rash and was thoroughly investigated by dermatology. The final diagnosis retained was a lichen or bullous pemphigoid-like eruption which was ultimately attributed to the immunotherapy, possibly triggered by concomitant use of celecoxib. The patient has last used celecoxib in September of 2019 and has since not taken any nonsteroidal anti-inflammatory drugs. There was no kidney involvement or other systemic toxicity noted at that time. Durvalumab was temporarily discontinued and restarted in January of 2020 while the patient remained on prednisone 10 mg daily indefinitely.

Presenting Concerns

In mid-May of 2020, 3 weeks following her last durvalumab infusion, the patient developed dry cough, dyspnea and fever. Approximately 10 days later, she presented to the emergency department (ER) with a deterioration of her symptoms and tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using nasopharyngeal swab polymerase chain reaction.

Clinical Findings

The patient weighed 68 kg with a body mass index of 24.4 kg/m² on admission and had no significant weight fluctuations during her hospitalization. Initial investigations revealed severe rapidly progressive acute kidney injury with refractory hyperkalemia for which the patient required conventional intermittent hemodialysis within 24 hours after initial presentation. Urinary output was preserved with an average of 50 ml per hour over 24 hours calculated via catheter before start of first dialysis session. A single dose of furosemide 40 mg intravenous was given for hyperkalemia within the first hour. The patient had normal kidney function prior to admission with a baseline serum creatinine of 50 μmol/L, did not have a prior history of kidney disease and had not taken any medications known to potentially cause kidney injury including over-the-counter drugs and herbal medicine. Her home medications included acetaminophen, atorvastatin, prednisone, calcium, vitamin D, pregabalin, and levothyroxine. She was however treated in March of 2020 with cloxacillin 1g 3 times per day for 7 days total for an infectious lymphadenitis with excellent clinical response and with 2 normal documented serum creatinine values (50 μmol/L and 45 μmol/L) in the month following treatment. No new rash or arthritis was found on physical examination during her stay. Her blood pressure remained stable without any significant fluctuations, including during her dialysis sessions; we defined significant hypotension as blood pressure < 90 mmHg systolic and hypertension as > 180 mmHg systolic). While multiple bilateral ground-glass opacities were present on chest X-ray, she did not require supplementary oxygen. Absolute lymphocyte count fluctuated significantly during her hospitalization with a nadir of 0.52 x 10⁹/L without eosinophilia. Urinalysis revealed leukocyturia (11-100 white blood cells per high power field [HPF]), microscopic hematuria (11-100 red blood cells per HPF) and significant proteinuria (protein/creatinine ratio: 0.441 g/mmol) but without other clinical features of a nephrotic syndrome. Eosinophilia was not tested. There were no casts on microscopic urinalysis. C3 and C4 complement levels were normal. A low anti-nuclear antibody titer (1/160) was present, but anti-neutrophil cytoplasmic autoantibodies, anti-glomerular basement membrane and anti-DNA were absent. C-reactive protein was elevated on admission (271.5 mg/L). A computed tomography of the kidneys was performed on the first day, showing no signs of hydronephrosis, hypertrophy or other abnormalities. A dedicated kidney ultrasound was not done.

Diagnostic Focus and Assessment

The left kidney was biopsied on day 7 of admission and revealed a histological pattern compatible with severe ATIN (Figure 1). In-situ hybridization and immunohistochemical staining for SARS-CoV-2 did not show the presence of the virus within the tissue.

Therapeutic Focus and Assessment

Oral prednisone at a dose of 2 mg/kg/day was initiated on day 11 of hospitalization and rapidly tapered to 1 mg/kg/day on day 17 upon recovery of kidney function, permitting discontinuation of hemodialysis treatments (Figure 2).

Follow-Up and Outcomes

The patient returned to her baseline clinically and was discharged 17 days after admission. Follow-up assessment revealed rapid and sustained continuous improvement in kidney function.
Discussion

This is the first report describing a temporal association between a viral respiratory infection, in this case SARS-CoV-2, and the development of severe ATIN in association with ICI use. Although the criteria required to demonstrate direct invasion of the virus remain uncertain,5-7 the absence of detectable SARS-CoV-2 within the kidney tissue by immunochemistry suggests that development of ATIN was not related to direct infection of kidney parenchyma by the virus. One possible hypothetical explanation is an immune regulation dysfunction induced by SARS-CoV-2 as described in other organs8 and amplified in the setting of anti-programmed death-ligand 1 (anti-PD-L1) therapy.

The majority of ATIN induced by ICI are seen within the first year of treatment, typically within 6 to 12 weeks for anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and within 3 to 12 months for anti-programmed cell death protein 1 (anti-PD-1).9 In this case, ATIN occurred 3 years after starting immunotherapy, although treatment was temporarily interrupted for cutaneous toxicity. It is important to note, however, that drug-induced bullous pemphigoid has been associated with acute interstitial nephritis10 and may indicate increased individual susceptibility to autoimmune toxicities.

Figure 1. (A) Renal histopathology revealing a severe diffuse neutrophil-rich tubulointerstitial inflammatory infiltrate on periodic acid-Schiff staining, and (B) Tubulitis is also present (*) with areas of focal necrosis (black arrow). Note. Within tubules, necrotic debris and inflammatory cells are noted without casts. Mild mesangial hypercellularity was also present within the glomeruli (not shown). Immunofluorescence did not reveal immunoglobulin or complement deposition within the glomeruli or tubulointerstitial compartment.

Figure 2. Evolution of serum creatinine over time in relationship with clinical events.
Note. Hemodialysis sessions are denoted by N.B. there are no creatinine values available between her baseline value (<60 μmol/L) and the rise noted a few days before admission (131 μmol/L).
Acute kidney injury is a frequent complication of COVID-19 and the spectrum of kidney disease associated is vast. There is, however, little literature currently available that describes acute interstitial nephritis in patients with COVID-19. One recent case that has been reported shows granulomatous acute interstitial nephritis in a patient with COVID-19 but with many other confounding factors such as use of amoxicillin/clavulanic acid during development of the acute interstitial nephritis along with eosinophilia and maculopapular rash. In that patient, the response to corticosteroids was also noted to be rapid and efficacious. According to our clinical experience, interstitial nephritis caused by ICI toxicity respond very promptly to corticosteroid therapy. Although the median time to creatinine improvement was not described, the most comprehensive study on the phenomenon reports a complete recovery rate of 40%. In conclusion, we believe that a viral infection, in this case SARS-CoV-2 has acted as a trigger in the development of ATIN through an immunoregulatory disbalance in a susceptible individual despite systemic corticosteroid treatment. The use of cloxacillin in the past months might have also contributed to the disruption in immunomodulation and further increased the individual’s susceptibility toward ATIN. The pro-inflammatory effect of a systemic viral infection may tip the delicate balance between self-tolerance and immunity in the setting of ICI therapy leading to cross-reactivity and subsequent ATIN. It has been shown that numerous autoimmune disorders can potentially be precipitated by the hyperinflammatory state caused by SARS-CoV-2. Furthermore, in organ transplantations, some viral infections may also lead to acute rejections. It is possible that there is some pathophysiologic overlap between these allograft dysfunctions and what we have observed. It is currently unclear if this represents a frequent mechanism leading to irAE in clinical practice but may warrant increased clinician surveillance of patients treated with ICIs in the setting of viral illnesses, especially relevant in today’s COVID-19 pandemic.

Ethics Approval and Consent to Participate
This case report is waived from institutional review board approval.

Consent for Publication
We obtained written informed consent from the patient for the publication of this case report.

Availability of Data and Materials
Not applicable.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References
1. Pan C, Liu H, Robins E, et al. Next-generation immuno-oncology agents: current momentum shifts in cancer immunotherapy. J Hematol Oncol. 2020;13(1):29.
2. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16(9):563-580.
3. Perazella MA, Shirali AC. Immune checkpoint inhibitor nephrotoxicity: what do we know and what should we do. Kidney Int. 2020;97(1):62-74.
4. Johnson DB, McDonnell WJ, Gonzalez-Ericsson PI, et al. A case report of clonal EBV-like memory CD4(+) T cell activation in fatal checkpoint inhibitor-induced encephalitis. Nat Med. 2019;25(8):1243-1250.
5. Freligh M, Erman A, Wechtersbach K, Pleško J, Avšič-Županc T, Koje N. SARS-CoV-2 virions or ubiquitous cell structures? actual dilemma in COVID-19 era. Kidney Int Rep. 2020;5(9):1608-1610.
6. Delsante M, Rossi GM, Gandolfini I, Bagnasco SM, Rosenberg AZ. Kidney involvement in COVID-19: need for better definitions. J Am Soc Nephrol. 2020;31(9):2224-2225.
7. Kudose S, Batal I, Santoriello D, et al. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol. 2020;31(9):1959-1968.
8. Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. Curr Opin Rheumatol. 2021;133(2):155-162.
9. Wanchoo R, Karam S, Uppal NN, et al. adverse renal effects of immune checkpoint inhibitors: a narrative review. Am J Nephrol. 2017;45(2):160-169.
10. Ganapathineedi B, Mehta A, Dande S, Shinde A, Barsky G, Sebro N. Bullous Pemphigoid with atypical skin lesions and acute interstitial nephritis: a case report and focused literature review. Am J Case Rep. 2019;20:212-218.
11. Szajek K, Kajdi ME, Luycks VA, et al. Granulomatous interstitial nephritis in a patient with SARS-CoV-2 infection. BMC Nephrol. 2021;22(1):19.
12. Cortazar FB, KibbelaarZA, Glezerman IG, et al. clinical features and outcomes of immune checkpoint inhibitor-associated AKI: a multicenter study. J Am Soc Nephrol. 2020;31(2):435-446.
13. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219-227.
14. Yu S, Su C, Luo X. Impact of infection on transplantation tolerance. Immunol Rev. 2019;292(1):243-263.
15. Martin-Gandul C, Mueller NJ, Pascual M, Manuel O. The impact of infection on chronic allograft dysfunction and allograft survival after solid organ transplantation. Am J Transplant. 2015;15(12):3024-3040.