***Nivolumab-associated acute glomerulonephritis: Case report and literature review***

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***Abstract***

Immune checkpoint inhibitors are changing the landscape of oncologic treatment as they are significantly improving treatment of multiple malignancies. These drugs have unique toxicity profile, known as immune-related adverse events (irAEs). Nivolumab, anti PD-1 antibody, is FDA-approved for treatment of melanoma, non-small cell lung cancer and kidney cancer and can cause a spectrum of autoimmune reaction. The adverse effect can occur at any organ system in the body, but most commonly affects colon, lung, liver or endocrine system. Although rare, kidneys also can be involved. Here, we present a case of nivolumab-induced autoimmune glomerulonephritis, successfully treated with discontinuation of nivolumab, systemic corticosteroid and hemodialysis. Microscopic examination revealed diffuse tubular injury with vacuoles and immune complex mediated glomerulonephritis. Although the patient received systemic corticosteroid for approximately 5 months, the immunosuppressive therapy did not compromise the anticancer effect of nivolumab. Based on our experience, high dose of steroid and hemodialysis may be required for months before presumptive decision of treatment failure is made.

***Key words:*** Immunotherapy; Immune checkpoint inhibitors; Nivolumab; PD-1 antibody; Renal cell carcinoma; Acute kidney injury; Autoimmune nephritis; Steroid

***Introduction***

The field of oncologic immunotherapy is expanding rapidly. Since its introduction into clinical application for treatment of melanoma[[1]](#endnote-1),[[2]](#endnote-2), immunotherapy has been studied in numerous trials for cancers at other organ systems. Although the treatment appears promising, immune checkpoint inhibition is associated with unique category of side effects, termed immune-related adverse events (irAEs)[[3]](#endnote-3).

Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T cells, B cells and NK cells. It binds to PD ligand 1 (PD-L1) on the cell surface of tumor cells, inhibits cancer cell apoptosis and down-regulates function of T cells[[4]](#endnote-4),[[5]](#endnote-5). Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody, designed to augment immunologic reaction against cancer cells and has been FDA-approved for patients with advanced melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma. The autoimmune dysfunction caused by nivolumab can affect any organ system including lung, colon, liver, endocrine system, kidney, skin and brain[[6]](#endnote-6). Although not as frequently affected as other organs, kidney injury can cause diverse sequelae and potentially limit further oncologic treatment options. The incidence of grade 3 or 4 kidney injury (elevated creatinine) was 0.3% in patients with melanoma and 2% in patients with renal cell carcinoma6.

In clinical practice, autoimmune adverse effects have been managed by treatment interruption, systemic corticosteroids in the first line, and TNF inhibitors or cytotoxic immunosuppressants in the second line. In this report, we present a case of nivolumab-induced glomerulonephritis, successfully treated with prolonged use of high-dose steroid and hemodialysis.

***Case report***

Our patient is a 70-year-old male with past medical history significant for oxygen-dependent chronic pulmonary obstructive disease (COPD), squamous carcinoma of the right vocal cord - treated with definitive radiation therapy in November 1998, and stage 3b chronic kidney disease (CKD) who was diagnosed with metastatic renal cell carcinoma in January 2013. The patient started pazopanib 600 mg daily in February 2013, with a good initial response. However, the medication was discontinued in December 2013 due to disease progression to the lungs and rib cage. He was then started on Nivolumab 3 mg/kg every 2 weeks in December 2013. His disease initially responded well to the treatment. During the 10 months period while he was on nivolumab, kidney tumors decreased by 19% and 13% in the right and left side respectively, adrenal masses decreased by 23% on both sides. He continued the treatment until October 27, 2014 when he was found to have an acute kidney injury (AKI) with creatinine level of 10.08mg/dL. Serum creatinine level one month before was 1.67mg/dL. The patient was admitted for evaluation and treatment for AKI. Other pertinent past medical history included left renal vein thrombosis for which he was taking enoxaparin. Patient had heavy smoking history, 120 pack-years; he quit smoking in January 2013. Pertinent positives in the review of system included generalized weakness, fatigue and loss of appetite. Physical exam was significant for 15 lbs weight gain and mild lower extremity edema. There was no flank pain nor costovertebral angle tenderness.

Upon admission, basic metabolic panel revealed sodium 135mMol/L, potassium 3.8mMol/L, chloride 95mMol/L, CO2 28mMol/L, BUN 58mg/dL and creatinine 10.08mg/dL. Urinalysis was positive for large amount of protein and hemoglobin. In microscopic exam of urine, there were 15-20 white blood cells, too-numerous-to-count red blood cells and 1-3 granular casts in high power field. Fraction excretion of sodium was 2.2%. Serum C3, C4 levels were within normal range. Hepatitis B surface antigen, hepatitis C antibody, antinuclear antibody, anti-double strand DNA antibody, glomerular basement membrane antibody, c-ANCA and p-ANCA were all negative. Ultrasound revealed solid masses in the interpolar region of right kidney and upper pole of left kidney which represented his known renal cell carcinoma. Otherwise, kidney sizes were within normal range and there was no evidence of hydronephrosis.

Due to lack of diagnosis, biopsy of right lower pole of kidney was performed on October 29, 2014. Light microscopic examination demonstrated diffuse tubular injury with vacuoles and immune complex mediated glomerulonephritis with cellular crescent and necrosis. There was moderate interstitial inflammation with lymphocytes. By immunoflorescence, there was diffuse granular mesangial staining for IgA, C3, kappa and lambda light chain. The specimen was also sent for electron microscopic exam. One glomerulus with severe cellular crescent was selected for exam and demonstrated several hump-like subepithelial deposits and no subendothelial deposits. There was partial podocyte foot processes effacement. Proximal tubules were flattened with simplified tubular epithelium and shorter microvilli. The pathologic exams confirmed the final diagnosis of acute toxic-type tubular injury and IgA-dominant acute post-infectious glomerulonephritis. Pictures of microscopic exams are presented in Figure 1.

Temporal relationship between nivolumab and acute kidney injury along with biopsy findings established a diagnosis of immunotherapy-induced acute kidney injury. Nivolumab was discontinued and methylprednisolone 40mg intravenously twice a day was initiated. The following day, serum potassium increased to 5.6mMol/L, creatinine and BUN were elevated to 11.01mg/dL and 63mg/dL respectively. Nephrology was consulted and hemodialysis was initiated. Methylprednisolone was increased to 40mg three times a day(1mg/kg/day). After the biopsy report, patient was started on pulse dose steroid, methylprednisolone 1gm intravenously daily for 3 days, followed by methylprednisolone 40mg intravenously three times a day. 4 days later, steroids were changed to oral prednisone 40mg twice a day and the patient was discharged on steroid and outpatient hemodialysis.

Follow-up and outcome

One month after the discharge, the patient was re-admitted with fever, rash, tachycardia and elevated white blood cell (WBC) count, consistent with systemic inflammatory response syndrome (SIRS). Source of infection was unclear as blood and urine cultures were negative. He was discharged after a short course of intravenous antibiotics. Dose of prednisone was increased at this time. Another month after the second hospitalization, patient was admitted again with fever, tachycardia and hypotension. Again, there was no compelling source of infection identified after extensive diagnositc work up. During the third hospitalization of 9 days, he received stress dose of steroid, hydrocortisone 100mg three times a day. Upon discharge, he resumed tapering course of steroid, starting with prednisone 60mg daily. Oral prednisone was completely tapered off at the end of February 2015. In April of 2015, his serum creatinine level was 1.81mg/dL and BUN was 13mg/dL. Hemodialysis was discontinued as of April 27, 2015. Last contact with the patient was on March 30, 2016 and his kidney function remained stable at the time. Serum creatinine change over the 6 months of treatment course is illustrated in Figure 2.

While recovering from nivolumab toxicity, patient did not receive any treatment for renal cell carcinoma. In spite of the prolonged systemic corticosteroid treatment, anti-tumor activity seemed to continue as the tumors in bilateral kidneys and adrenal glands decreased in sizes for 18 months (Left adrenal gland: 3.7 to 2.4cm, Right adrenal gland: 7.0 to 5.8cm, Left kidney mass: 6.0 to 3.4cm, Right kidney mass: 7.0 to 5.8cm in diameters). In March of 2016, patient started axitinib 3mg twice a day for symptomatic disease progression (worsening of rib lesion).

***Discussion***

Immune-related adverse events (irAEs) are encountered more frequently in daily oncologic practice as the use of immune checkpoint inhibitors is expanding. Immune checkpoint inhibition involves two major transmembrane proteins, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-protein 1 (PD-1). Nivolumab, monoclonal anti PD-1 antibody, blocks T cell inhibition and stimulate immunologic response toward cancer cells, but it may also impair self-tolerance of immune system. This potential side effect can occur in any organ of the body, but it is known to predominate in gastrointestinal tract, lung, liver and endocrine system[[7]](#endnote-7).

Table 1 summarizes available case reports identified in literature review. Several articles reported successful treatment of ipilimumab-associated nephritis with systemic steroid. Fadel et al. reported a case of lupus nephritis which occurred after use of ipilimumab and resolved after steroid treatment[[8]](#endnote-8). 6 other cases of ipilumumab-associated nephritis were reported[[9]](#endnote-9),[[10]](#endnote-10),[[11]](#endnote-11),[[12]](#endnote-12). In addition, there were 3 cases of AKI caused by anti PD-1 antibody. 2 patients who had nivolumab-related kidney injury were successfully treated with steroids[[13]](#endnote-13), and 1 patient who developed pembrolizumab-related kidney injury had improvement of nephritis after steroid[[14]](#endnote-14).

In clinical trials of nivolumab or other anti PD 1 antibodies, renal system was not affected as frequently as other organ systems. In a population of patients with NSCLC, 5 out of 287 patients (2%) who were treated with nivolumab developed elevated serum creatinine, 2 of them (0.7%) had renal failure[[15]](#endnote-15). Among the patients with melanoma treated with pembrolizumab (anti PD-1 antibody), 1 out of 277 patients (0.4%) experienced nephritis with renal failure14. Another anti PD-1 antibody, lambrolizumab, was associated with renal failure in 3 out of 135 patients (2%) with melanoma, 2 of the 3 patients had grade 3 or 4 adverse events[[16]](#endnote-16).

Although alteration in immunologic self-tolerance theoretically accounts for the renal dysfunction, specific mechanism has been diverse among the existing case reports. Biopsy results also varied. One patient was diagnosed with lupus nephritis during the treatment with ipilimumab8. The diagnosis was made based on positive antinuclear antibody and anti-double-strand DNA antibody. Electron microscopy confirmed the presence of granular, electron-dense extramembranous deposits. Izzedine et al. reported 2 cases of acute interstitial nephritis (AIN) associated with ipilimumab11. In a more recent case reported by Thajudeen et al., the biopsy also revealed granulomas and interstitial infiltration with lymphocytes, eosinophils and plasma cells12. In our case, biopsy revealed acute tubular injury and immune complex mediated glomerulonephritis.

Acute interstitial nephritis (AIN) from ipilimumab was suggested as a possible etiology of kidney failure in previous case reports11. However, in our case review, there was no sign or symptom consistent with AIN, such as fever, rash or eosinophilia. Autoimmune glomerular injury was determined as another major component of etiology in our case, based on (a) glomerular immune deposits identified in the biopsy specimens, (b) temporal relationship between the use of immune checkpoint inhibitors and the onset of acute kidney injury, and (c) lack of evidence of any other cause of glomerulonephritis. Within the boundaries of our knowledge, this is the first case of nivolumab-associated glomerulonephritis with confirmative light microscopic and electron microscopic findings.

Regardless of the etiology or biopsy result, kidney function generally improved after treatment with steroid. There was no case in our literature review in which TNF inhibitors or cytotoxic immunosupressants were required. In some of the cases reviewed, immunotherapy was resumed after kidney function improved. In our case, nivolumab was permanently discontinued and the patient stayed on a lengthy tapering course of steroid for approximately 4 months. Even after the prolonged used of systemic corticosteroid and discontinuation of nivolumab, immunologic anti-tumor effect seemed to persist. The tumors in his kidneys shrunk in sizes. In our literature review, there was a case of melanoma patient who experienced continued tumor regression in spite of discontinuation of ipilumumab and daily administration of systemic corticosteroid.[[17]](#endnote-17) In another case of melanoma treated with ipilimumab, both steroid and infliximab were used for grade 3 colitis, but there was no progression of disease after approximately 3 years[[18]](#endnote-18). In a clinical trial, corticosteroid for treatment of irAEs did not impact clinical activity of ipilimumab in advanced melanoma[[19]](#endnote-19).

The patient in our case was re-admitted twice with unexplained systemic inflammatory response syndrome (SIRS). Both hospitalizations occurred while the dose of prednisone was tapered down. In spite of extensive diagnostic tests for infection, there was no clear source of SIRS. Pyrexia has been reported as one of the side effects of immunotherapy in clinical trials, but our patient had severe cases of SIRS with hypotension requiring admission to intensive care unit. Although possible relationship between immunotherapy and SIRS is intriguing, more evidence should accumulate to link autoimmunitiy with occurrence of SIRS and hemodynamic shock.

In summary, use of systemic corticosteroid has been generally successful in achieving optimal treatment response for immunotherapy-associated renal dysfunction. Drug manufacturer recommends 0.5 to 1mg/kg/day prednisone equivalents for grade 2 or 3 renal dysfunction, and if no improvement occurs, 1 to 2 mg/kg/day prednisone equivalents and discontinuation of nivolumab. For life threatening, grade 4, renal dysfunction, recommendation is to start 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue nivolumab7. Based on our experience, pulse dose of steroid can be used for resistant renal dysfunction to the above dosage. Although treatment response may not be ostensible initially, presumptive decision of treatment failure should be avoided. As in our case, patients may require prolonged course of systemic corticosteroid and hemodialysis, and kidney function may improve months later.

***List of abbreviations***

irAEs, immune-related adverse events; PD-1, programmed cell death 1; PD-L1, PD ligand 1; NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; AKI, acute kidney injury; SIRS, systemic inflammatory response syndrome; CTLA-4, cytotoxic T-lymphocyte antigen 4; AIN, acute interstitial nephritis; AFB, acid-fast bacillus; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis

***Competing interests***

None declared

Figure 1. Microscopic examinations of kidney biopsy specimen



(a) & (b) Hematoxylin and eosin stain of kidney biopsy specimen revealed interstitial infiltrate with tubular injury (Arrows), and glomerulitis with cellular crescent (Arrowhead) and mesangial proliferation (Arrow)

(c) Immunoflorescence stain for IgA deposits

(d) Electron microscopic picture of subepithelial deposit (Arrow)

Figure 2. Serum creatinine change over 6 months



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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | No. of patients | Age | Gender | Medication | Cancer | Kidney biopsy | Treatment | Outcome |
| Fadel et al.8  2009 | 1 | 64 | M | Ipilimumab | Melanoma | Extramembranous and mesangial deposits of immunoglobulin (consistent with lupus nephritis) | Steroid | Resolved |
| Forde et al.9  2012 | 1 | 59 | M | Ipilimumab | Melanoma | Not available | Steroid  No dialysis | Resolved |
| Voskens et al.10  2013 | 1 | 53 | F | Ipilimumab | Mucosal | Not available | Steroid | Resolved |
| 2 | 72 | F | Ipilimumab | Unknown primary | Not available | Steroid | Resolved |
| Izzedine et al.11  2014 | 1 | 72 | M | Ipilimumab | Melanoma | Interstitial inflammation and polynuclear infiltration in glomerulus | Steroid | Resolved |
| 2 | 60 | F | Ipilimumab | Melanoma | Tubulo-interstitial inflammation with necrosis and two non-necortizing granulomas | Steroid | Resolved |
| Thajudeen et al.12  2015 | 1 | 74 | M | Ipilimumab | Melanoma | Interstitial edema with infiltrate of lymphocytes and granulomas | Steroid | Resolved  Ipilimumab resumed |
| Vandiver et al.13  2016 | 1 | 58 | F | Nivolumab | Melanoma | Not available | Steroid | Resolved |
| Hofmann et al.14  2016 | 1 | 52 | M | Nivolumab | Melanoma | Not available | Steroid and normal saline | Resolved  Nivolumab resumed |
| 2 | 73 | M | Pembrolizumab | Melanoma | Not available | Steroid | Improved |

Table 1. Reports of immunotherapy associated renal adverse events and treatment

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