CASE REPORT

Polyomavirus nephropathy of the native kidney in a patient with rheumatoid arthritis and pulmonary fibrosis

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Accepted 18 August 2015

SUMMARY

Polyomavirus nephropathy is commonly seen in the renal allograft setting but is uncommon in native kidneys. This paper describes polyomavirus nephropathy that developed in the native kidneys of a patient following immunosuppressive therapy for rheumatoid arthritis/Sjögren's syndrome associated lung disease. The patient presented with dyspnoea and a slow steady rise in serum creatinine. Owing to chronic immunosuppression, calcineurin-inhibitor toxicity was suspected. However, renal biopsy revealed polyomavirus nephropathy. The treatment of choice, lowered immunosuppression, was complicated by exacerbation of the patient's lung disease. This case highlights features of polyomavirus nephropathy in the native kidney, as well as the difficulty in its treatment when immunosuppressive treatment is necessary for medical comorbidities.

BACKGROUND

Polyomavirus nephropathy (PVN) is typically caused by reactivation of infection with BK virus, a member of the polyomavirus family. It is characterised by tubulointerstitial nephritis and renal impairment. In the general population, 60–90% of individuals have serological evidence of exposure to BK virus.^{1 2} The virus remains latent in the urothelium and renal tubular epithelial cells, and reactivation can be seen in cases of relative or absolute immunosuppression, including diabetes, pregnancy or malignancy. In these instances, reactivation is usually limited to the urothelium, and kidneys are typically spared from clinically significant infection.³ However, in the renal transplant setting, PVN is an important cause of allograft failure. BK virus is the most common viral infection in the renal allograft, and the prevalence of BK PVN is approximately 1–8%.⁴ Treatment of BK nephropathy consists of decreasing immunosuppression and, possibly, addition of antiviral agents. Early diagnosis is important so that changes in immunosuppression can be implemented, which can improve renal function, decrease interstitial fibrosis and slow overall disease progression.⁵

PVN has been only rarely described in the native kidney.^{3 6–10} Owing to the small number of cases, it is not certain whether histology, prognosis and optimal treatment for BK PVN differ in native kidneys and renal allografts. Careful description of pathological features and clinical course of such patients will be useful in understanding this disease in the native organ. We describe a patient with

rheumatoid arthritis (RA) and associated interstitial lung disease (ILD) who was treated with immunosuppression and found to have PVN. We believe this case illustrates several important features of this disease and its response to therapy.

CASE PRESENTATION

A 55-year-old man with a history of RA and associated ILD was admitted for worsening dyspnoea and increased serum creatinine (SCr). The Medical history was significant for bronchiolitis obliterans, Sjögren's syndrome, chronic kidney disease and hypertension. Medications included tacrolimus and mycophenolate mofetil (MMF) for over 6 years. SCr on admission was 2.19 mg/dL (194 µM), compared to his baseline of approximately 2 mg/dL (177 µM). On examination, the patient had inspiratory and expiratory wheezing in the left base and right lateral lung fields. He was noted to have 1+ bilateral ankle oedema. Cardiovascular examination was within normal limits. Vitals were as follows: blood pressure, 145/76 mm Hg; temperature, 36.4°C; pulse, 99 bpm and respirations, 16 breaths/min. Laboratory values on admission included: blood urea nitrogen, 25 mg/dL (8.9 mM); SCr, 2.19 mg/dL (194 µM); albumin, 3.2 g/dL; haemoglobin, 9.6 mg/dL and tacrolimus level, 2.6 ng/mL (range: 5–15 ng/mL). Urinalysis showed no proteinuria or haematuria. Renal ultrasound showed normal-sized kidneys with mildly increased echogenicity and no hydronephrosis. Intravenous meropenem was started for bronchiolitis exacerbation. The patient received 100 mL/h of normal saline. Additionally, outpatient medications, tacrolimus, MMF and prednisone were continued. Renal function continued to deteriorate over the next 6 days, with SCr reaching 3.05 mg/dL (270 µM). Calcineurin-inhibitor (CNI) toxicity was suspected. A kidney biopsy was performed on day 6 of admission.

INVESTIGATIONS

Renal biopsy revealed renal cortex with diffuse tubular injury, including cytolysis, sloughed cells and reactive nuclear change (figure 1A). These changes were accompanied by a predominantly mononuclear interstitial immune cell infiltrate with tubulitis and occasional clusters of plasma cells. Numerous intranuclear inclusions were identified within tubular epithelial cells (figure 1A). Immunostain for SV40 T antigen, which also recognises BK polyomavirus, showed numerous positive tubular epithelial nuclei (figure 1B). Immunostain for cytomegalovirus was negative. There was

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To cite: Krystel-Whittemore M, McCarthy ET, Damjanov I, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211564

Figure 1 Polyomavirus nephropathy, first biopsy specimen. (A) Periodic-Acid Schiff stain demonstrating injured tubules and viral intranuclear inclusions (arrow; scale bar=25 µm); (B) immunohistochemical stain for SV40 large T antigen detects BK polyomavirus within tubular epithelial nuclei (scale bar=25 µm); (C) direct immunofluorescence for IgG revealing tubular basement membrane staining; (D) transmission electron micrograph showing uniform viral particles within tubular epithelial nucleus (scale bar=100 nm).

moderate interstitial fibrosis (approximately 40% of cortex). Definitive features of acute and/or chronic CNI toxicity were not identified. Immunofluorescence microscopy showed granular 2–3+ staining of tubular basement membranes for IgG (figure 1C) and C3. Electron microscopy demonstrated uniform viral particles approximately 40 nm in diameter within tubular nuclei (figure 1D). The diagnosis of PVN stage/class B¹¹ was made. Subsequent to biopsy, PCR for BK polyomavirus revealed 34×10^6 copies/mL in plasma and 20×10^9 copies/mL in urine.

TREATMENT

Following the diagnosis of PVN, lowered immunosuppression was considered. However, there was concern for worsening ILD, so the patient was treated with oral ciprofloxacin 500 mg two times per day and intravenous immunoglobulin (IVIG). He received these treatments for 2 weeks without significant improvement in renal function. Two months after original admission, leflunomide 10 mg/day was added to his treatment regimen and MMF was decreased from 1500 mg two times per day to 1000 mg two times per day. Tacrolimus was continued at 2 mg two times per day. Renal and pulmonary function remained stable. SCr at this time was 2.83 mg/dL (250 µM). PCR for BK polyomavirus revealed a small decline in viral load: 17×10^6 copies/mL in plasma and 3.8×10^9 copies/mL in urine. MMF dose was further decreased after 1 week to 750 mg two times per day.

OUTCOME AND FOLLOW-UP

Two weeks after the change in MMF to 750 mg two times per day, the patient presented with worsening dyspnoea and fatigue. He denied any urinary symptoms, and his SCr was 2.75 mg/dL (243 µM). On examination, he had bilateral wheezes and right basilar rales. Chest CT scan showed persistent mild-to-moderate diffuse bronchiectasis with slight increase in mild scattered infiltrates and moderate peribronchial thickening. He was started on levofloxacin and oral corticosteroids for bronchiolitis obliterans exacerbation. ECG showed atrial fibrillation. SCr slowly increased to 5.93 mg/dL (524 µM) by hospital day 9. Urinary sediment was bland. BK viral loads in plasma and urine were 11×10^6 copies/mL

and 6×10^9 copies/mL, respectively. Acute kidney injury was initially attributed to acute tubular necrosis in a setting of atrial fibrillation. The patient required haemodialysis, but after control of atrial fibrillation, renal function improved and haemodialysis was no longer necessary. In light of decline in renal function, repeat kidney biopsy was obtained 17 days after admission. Histology on repeat biopsy demonstrated PVN that was not significantly changed from the initial biopsy. Once again, it was decided that withdrawal of immunosuppressive medications was not feasible because of the patient's significant lung disease. Over the next 5 months, his BK titre declined to 250 000 copies/mL in plasma, but his SCr remained near 4 mg/dL (354 µM).

DISCUSSION

Polyomaviruses comprise of a family of non-enveloped DNA viruses with icosahedral capsids. BK and JC polyomaviruses are known to cause human disease. By early childhood, up to 60–90% of the population shows seropositivity for BK virus.² Initial infection is typically asymptomatic but can present with upper respiratory symptoms or cystitis.⁴ After initial infection, the BK virus remains latent in the urothelium and renal tubular epithelial cells. Pathological manifestations typically occur after reactivation.

BK PVN in the renal allograft

BK virus reactivation is usually precipitated by immunosuppression in association with renal transplantation. Reactivation of latent BK virus can result in urinary tract disease, including PVN, cystitis and ureteral obstruction,¹² with PVN being most common. Reactivation is very common in the post-renal transplant setting, with overall prevalence of BK viraemia and viremia of 57% and 29%, respectively.⁴ PVN is much less common, with PVN developing in approximately 1–8% of patients with evidence of reactivation.² Of note, cases of PVN in patients on tacrolimus and MMF are 13 times more prevalent compared to patients not on those medications.² PVN accounts for allograft failure in 1–10% of patients.¹³

BK PVN pathology

Histological manifestations of PVN include tubulointerstitial nephritis and tubulitis characterised by focal necrosis and/or cytolysis of tubular epithelial cells, with tubular basement membrane denudation.^{13 14} On reactivation, the viral genome is replicated in the host cell nucleus, and intranuclear inclusions can be seen within tubular epithelial cells and occasionally glomerular parietal epithelial cells. Virus can be detected by immunohistochemistry with antisera directed against SV40 large T antigen, which recognises the polyomavirus family, and by electron microscopy.

The Banff working proposal for histological classification of PVN defines three stages.¹⁵ Stage A is characterised by limited viral replication with intranuclear inclusions, minimal cytopathic changes, and minimal to moderate fibrosis and atrophy (<50% of cortical area). Infection may be limited to local medullary involvement. Stage B shows marked viral replication, with extensive cytopathic effects, and minimal to moderate fibrosis and atrophy. Stage C is characterised by significant interstitial fibrosis and tubular atrophy (>50% of cortical area), and minimal to marked viral replication and cytopathic effects. The clinical utility of this system is currently being evaluated.

BK PVN treatment

Reduction of immunosuppression is the mainstay of treatment for PVN.¹⁶ Antiviral treatment is an active area of investigation. Several small studies have suggested cidofovir to be clinically

beneficial.^{17–19} However, in these studies, immunosuppression was also decreased, so it is difficult to tell which factor improved allograft function. Fluoroquinolones have been used to treat BK PVN in patients.²⁰ Despite some successful case reports²¹ and suggestion of efficacy in a retrospective trial,²² controlled prospective trials have not shown significant benefit.^{23–24} Leflunomide, an immunomodulatory drug that inhibits de novo pyrimidine synthesis, may provide benefit for PVN in allografts when added to reduction in immunosuppression.^{25–28} However, there are reports of only limited efficacy.²⁹ Administration of IVIG along with reduction of immunosuppression may benefit patients with PVN;³⁰ however, there is mixed evidence supporting the use of IVIG alone.^{30–31}

Combinations of these therapies may hold promise. Leflunomide combined with IVIG and decreased immunosuppression resulted in prolonged graft survival in one study of 214 patients.³² Another study showed resolution of BK viraemia in 27/30 patients after addition of IVIG in patients who had inadequate response to reduction in immunosuppression and leflunomide.³³ Additionally, one study showed that treatment with a combination of ciprofloxacin and leflunomide with a slight decrease in immunosuppression resulted in a decrease in BK viral load and improved estimated glomerular filtration rate.³⁴

BK PVN in the native kidney

There are only a few descriptions of BK PVN in native kidneys in the literature. A small series of eight cases has been reported in which six patients had haematological malignancies and were receiving chemotherapy, one patient had cystic fibrosis requiring lung transplant and one had pulmonary tuberculosis.³ Treatments included leflunomide, cidofovir, fluoroquinolones and IVIG, but it was not possible to make significant reductions of immunosuppression in these patients. Response to therapy was disappointing. Six had continuing decline in renal function, two of whom required dialysis. Three patients died from malignancy, renal failure or infection.

The remaining literature regarding PVN in the native kidney consists of case reports. A 10-year-old boy with acute lymphoblastic leukaemia presented with PVN after chemotherapy and was successfully treated with IVIG.⁷ A 73-year-old man with a history of chronic lymphoblastic leukaemia and pulmonary fibrosis treated with prednisolone developed PVN. Leflunomide decreased the serum viral load and improved renal function.⁸ A 67-year-old woman developed renal failure due to PVN 5 years after lung transplantation, and was treated with decreased immunosuppression and leflunomide, which improved renal function.⁶ A 7-year-old boy with a heart transplant presented with PVN 6 months after his second transplant. Despite a small decrease in immunosuppression and the addition of cidofovir, renal failure progressed.¹⁰ A recent case report described PVN in the native kidney of a patient after allogeneic haematopoietic stem cell transplant.⁹ The antiviral, brincidofovir, was administered without altering the level of immunosuppression. Subsequently, BK viraemia decreased significantly. Kidney function was maintained and dialysis was not required for 11 months prior to his death from unrelated causes.

Summary

To the best of our knowledge, this is the first report of BK nephropathy in a patient being treated for RA-associated ILD. This case illustrates many salient features associated with BK nephropathy, namely, development in setting of significant immunosuppression and the difficulty in treating it in the face

of continued immunosuppression. Optimal therapy for patients who cannot tolerate decrease in immunosuppressive medications is unclear at this time. Also, it remains to be seen whether BK nephropathy in native kidneys follows the same clinical course as in renal allografts, including response to current and future therapies.

Learning points

- ▶ While rare, polyomavirus nephropathy (PVN) can be seen in the native kidney in patients with immunosuppression. It is important to keep this in the differential diagnosis for immunocompromised patients with renal dysfunction.
- ▶ The most straightforward and effective treatments for PVN, namely, regimens that include lowering immunosuppression, are not always possible due to comorbidities.
- ▶ Renal biopsy can be a critical tool for directing appropriate therapy in immunocompromised patients with renal dysfunction.
- ▶ Combination therapies, including those with newer antivirals, may hold promise for treatment of PVN.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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