INTRODUCTION

BK virus was first detected in the urine of a renal transplant recipient in 1971 and was named after the recipient. BK virus is usually acquired in childhood via respiratory transmission, and remains in the uroepithelium of immunocompetent individuals. The seroprevalence in adults is 82% to 99%, with low-level viruria seen in 5% to 20% of immunocompetent individuals and up to 80% of patients after stem cell transplantation, manifesting as asymptomatic hemorrhagic cystitis in a minority (4%–25%) or, rarely, as mortality. Polyomavirus nephropathy is known to complicate the cases of up to 10% of renal transplant recipients, sometimes leading to graft failure. In non–renal transplant recipients including those who have undergone solid organ and stem cell transplantation, polyomavirus nephropathy has been reported increasingly with improvement in detecting methods.

CASE PRESENTATION

A 56-year-old patient of Caucasian/white ethnicity was diagnosed with multiple myeloma in 2006. He was initially treated with vincristine, dexamethasone, and adriamycin, and eventually underwent autologous stem cell transplantation. Two years later, he had a relapse that was treated with dexamethasone, cyclophosphamide, and thalidomide, followed by a second autologous stem cell transplantation. He relapsed again after 2 years and received lenalidomide and dexamethasone along with cyclophosphamide 500 mg weekly to improve response. As per the standard myeloma approach, his chemotherapy regimen was planned to continue long term until disease progression. During his course of disease, he sustained a number of infectious complications, including cellulitis and osteomyelitis with bacteremia in 2015 and 2016, and pneumocystis pneumonia treated with sulfamethoxazole-trimethoprim. All infections were treated with total resolution. Two months after resolution of his pneumocystis pneumonia, he developed a left-leg deep vein thrombosis and, on evaluation, was noted to have an increase in serum creatinine from 85 μmol/l to 241 μmol/l. He was started on low–molecular-weight heparin for the deep vein thrombosis, and, with the potential of a drug-related cause of the renal dysfunction, lenalidomide, cyclophosphamide, rosuvastatin, and sulfamethoxazole-trimethoprim were held and further investigations were performed. His myeloma-related paraprotein and light chains in both serum and urine were stable and did not indicate progressive myeloma. A renal Doppler ultrasound showed normal vasculature without evidence of urinary obstruction or renal vein thrombosis. Despite withdrawal of the potentially offending drugs, there was no improvement in renal function over the subsequent 6 to 8 weeks, and a renal biopsy was performed.

Light microscopy revealed diffuse marked lymphocytic interstitial inflammation with tubulitis and viral cytopathic change on a background of severe fibrosis, and immunohistochemistry for SV40 LT-ag showed diffuse positivity (Figures 1–4). Glomeruli were shrunken but otherwise unremarkable, and immunofluorescence was negative.

Subsequent blood BK virus polymerase chain reaction showed 3.72E+4 copies/ml, and urine polymerase chain reaction for BK virus was 3.13E+8 copies/ml. The transplant infectious disease team started leflunomide 20 mg daily, subsequently increased to 40 mg, along with reduced immunosuppression. Cidofovir was not used because of advanced renal dysfunction. Because lenalidomide is excreted...
largely by the kidneys, the patient’s myeloma therapy was switched to ixazomib and dexamethasone. Unfortunately, however, after 6 months, the serum creatinine remains elevated at 327 µmol/l and BK virus viral load at 2.94E+4 copies/ml.

**DISCUSSION**

In nonrenal solid organ or stem cell transplant recipients, BK virus infection complicates the clinical course of recipients by causing hemorrhagic cystitis in 5% to 15% and polyomavirus nephropathy in fewer patients, ranging from mild to severe, with renal failure requiring renal replacement therapy. BK virus disease is associated with the total cumulative immunosuppression to which the patient has been exposed, as well as the specific immunosuppressive agents used. Steroid exposure independently is associated with increased BK viruria and our patient had received dexamethasone multiple times, which is known to cause increased viral replication in vitro. A study of pediatric allogeneic stem cell transplantation has shown that blood BK virus polymerase chain reaction results of >10,000 copies/ml predict worse renal outcomes. According to a recent meta-analysis, the risk of developing chronic kidney disease in hematopoietic stem cell transplantation recipients is 16%, with the risk of needing renal replacement therapy being less than 1%. The majority of cases have been labeled as “bone marrow transplant nephropathy,” with the remaining being considered as “uncertain in origin.” A percentage of these could potentially be due to undiagnosed polyomavirus nephropathy, although this has not been documented or reported, likely because polyomavirus nephropathy was not considered in the differential diagnosis.

Allogeneic stem cell transplant recipients are considered at higher risk than autologous stem cell
transplant patients for chronic kidney disease, because the latter receive less immunosuppression with no calcineurin inhibitors, and do not develop graft-versus-host disease or veno-occlusive disease.

Polyomavirus nephropathy in renal transplant patients is characterized by high-level viral replication and significant inflammatory response healing with fibrosis and tubular atrophy, the final common irreversible pathway to renal failure. In a recent publication by Inazawa et al., BK virus replication in blood was not seen in 24 patients in the first 42 days after autologous stem cell transplantation.

Sanchez-Pinto et al. had published a case report of a 10-year-old pediatric patient whose clinical course after autologous stem cell transplantation was complicated by development of BK viremia after 2 months and frank nephropathy as evidence from renal biopsy at 5 months.19 To our knowledge, there has been only 1 case report with polyomavirus nephropathy in an adult patient with autologous stem cell transplantation for lymphoma.20

Our case presents with several teaching points (Table 1). The diagnosis was based on renal biopsy, which is considered the gold standard for polyomavirus nephropathy diagnosis.

The uniqueness of this case was that polyomavirus nephropathy was not suspected, because the patient had undergone autologous stem cell transplantation and there were other possible offending factors temporally associated with the onset of renal dysfunction. However, as acute kidney injury persisted after correcting the presumed factors, a renal biopsy was performed, ultimately revealing polyomavirus nephropathy. Our patient, over the course of 10 years, had received multiple immuno-suppressive regimens for myeloma, and the occurrence of multiple infectious complications attests to his persistent immuno-suppressed state. In particular, he had received cyclophosphamide, which has been reported as a risk factor for development of BK viruria and hemorrhagic cystitis in hematopoietic cell transplantation.12 Based on the current literature, there are no recommendations for surveillance or monitoring for polyomavirus nephropathy in stem cell transplantation; thus, the diagnosis can be made only by a renal biopsy. Given the pathogenic mechanisms of BK virus and the biopsy findings of severe interstitial fibrosis and tubular atrophy, we predict that our patient is unlikely to recover at this point. This case illustrates the importance of considering polyomavirus nephropathy within the differential diagnosis of unexplained renal failure in chronically immuno-suppressed patients, so that timely diagnosis can be performed, allowing the potential for renal recovery.

**DISCLOSURE**

All the authors declared no competing interests.

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