Nephropathy Evolving Within the First Two Posttransplant Months With No Typical Cytopathic Lesions: Two Cases Presentation

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ABSTRACT

Background. We report 2 cases of polyomavirus-associated nephropathy (PyVAN) emerging within the initial 8 posttransplant weeks. These cases were characterized by intraepithelial BK virus replication without typical nuclear inclusions in epithelial cells.

Methods and Results. A 70-year-old male recipient of a cadaveric kidney transplant had experienced unsatisfying graft function since the time of transplantation (Tx). One month after Tx, results of a graft biopsy revealed mild tubulointerstitial inflammation. No intraepithelial nuclear inclusions suggestive of viral infection were present at that time. The patient received intravenous methylprednisolone, and the dosage of tacrolimus was increased. Due to a further drop in the glomerular filtration rate, a subsequent kidney biopsy was performed during posttransplant week 10, which revealed lesions typical of PyVAN. Retrospectively performed SV40 staining revealed that intragraft polyomavirus replication was already present on posttransplant day 30. Basic immunosuppression reduction and ciprofloxacin administration were followed by BK viremia elimination, stabilization of graft function, and resolution of PyVAN. In another patient, a 62-year-old male recipient of a cadaveric renal graft, BK viremia was monitored from the time of Tx. Two months after Tx, the patient was found to have a BK viral load of 6×4 $\log^{10}$/mL. Results of the graft biopsy revealed fully preserved tubular epithelium, but SV40 staining was positive in some of these cells. After basic immunosuppression reduction and introduction of ciprofloxacin, the BK viral load dropped to $1 \times \log^{10}$/mL with graft function stabilization.

Conclusions. PyVAN may emerge as early as 4 weeks after Tx, with near-normal or acute rejection–like graft morphology. The early monitoring of plasma BK viral load, as well as SV40 staining, avoids misdiagnosis of this severe posttransplant complication.

THE MOST commonly known human polyomavirus in organ transplant recipients is polyomavirus BK (BKPyV), which has been linked to polyomavirus-associated nephropathy (PyVAN) in kidney transplants. The virus is ubiquitous in adults, as indicated by seroprevalence rates >80% worldwide [1]. After primary infection, BKPyV establishes latency, mainly in the renal tubular epithelial cells and uroepithelium. It is also tropic for peripheral blood leukocytes and probably other sites, such as the brain, liver, lung, and eye. It has been claimed that BKPyV reactivation occurs in 20% to 40% of kidney transplant recipients between week 5 and month 17 after transplantation. Approximately 10% to 20% of renal graft recipients have BKPyV present in the circulation, and 30% to 50% develop PyVAN, usually manifesting within 4 to 12 weeks after the onset of viremia [2].

Morphologically, PyVAN is characterized by the presence of acute tubular injury manifested by virally induced lysis and necrosis of tubular epithelium as well as by the occurrence of intranuclear viral inclusion bodies within the

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epithelium. These intranuclear inclusions represent a collection of virions and constitute the most characteristic of all tubular lesions evolving in a course of PyVAN [3]. The tubulointerstitial infiltration with granulocytes and lymphocytes usually occurs 8 weeks after detection of viremia. Without intervention, from 15% to >90% of kidney transplant recipients progress to allograft failure, which in at least 50% of cases is followed by graft loss. The major risk factor for PyVAN is the high overall degree of immunosuppression. An increased risk of PyVAN has also been attributed to acute rejection episodes, low or absent BKPyV-specific T-cell responses, older recipient age, deceased donation, prolonged cold ischemia time, ureteric stents, male sex, and HLA mismatch [4,5]. The management of patients with PyVAN is not well established because there are no BKPyV-specific antiviral drugs for prophylaxis or treatment. In most cases, the treatment is based on the reduction of maintenance immunosuppression.

We report 2 cases of PyVAN emerging within the first 8 posttransplant weeks, characterized by intraepithelial BKPyV replication without typical nuclear inclusions in epithelial cells.

CASE 1

A 70-year-old male patient with end-stage renal failure secondary to autosomal dominant polycystic kidney disease received his first kidney transplant from a 67-year-old, 3/6 HLA-matched deceased female donor. Before transplantation, the panel reactive antibody level was 0. The donor was cytomegalovirus (CMV) IgG-positive, CMV IgM negative, hepatitis C virus negative, and hepatitis B virus negative. The recipient was CMV IgG positive, CMV IgM negative, CMV DNA negative, Epstein-Barr virus (EBV) viral capsid antigen (VCA) IgG positive, EBV VCA IgM negative, and EBV Epstein-Barr nuclear antigen (EBNA) IgG positive. Because BK virus (BKV) serologic screening is not routinely performed, the pretransplant BKV status of the donor and each kidney recipient was not known. The posttransplant immunosuppressive regimen consisted of steroids, tacrolimus, mycophenolate mofetil (2000 mg), and basiliximab. Results of the implantation biopsy revealed acute tubular necrosis, arteriosclerosis, and arteriolar hyalinization. Due to delayed graft function, a second graft biopsy was performed on day 14, which revealed the same morphologic picture as the implantation biopsy. On posttransplant day 30, due to persistently poor graft function, a third biopsy was performed, which revealed mild tubulointerstitial inflammation, fulfilling the criteria for recognition of the Banff category suspicious for rejection (Fig 1). The lack of typical intranuclear inclusions and very short time after transplantation spoke against the perception that lesions encountered might have been related to BKPyV replication, and SV40 staining was not performed. The patient received methylprednisolone (3 × 250 mg intravenously), and the tacrolimus dosage was increased (kept at a target trough level >9 ng/mL). Due to an additional drop in glomerular filtration rate, a fourth kidney biopsy was performed during posttransplant week 10. Other than mild tubulointerstitial mononuclear cell inflammation, this biopsy specimen revealed focal tubular lesions in the form of epithelial cell necrosis and nuclear inclusions. The presence of inclusions raised the suspicion of PyVAN. Immunohistochemical staining against antigen SV40 revealed BKV replication in many of the cortical and medullary tubular epithelial cells. At that time, plasma BK viremia was evaluated and revealed a BK viral load of 7×4 $\log^{10}$/mL. These findings made us reevaluate the previous 3 biopsy specimens with SV40 staining. Results of the implantation biopsy and the biopsy performed on posttransplant day 14 were SV40 negative. Retrospectively, we ascertained that BKV replication was present in the sample from the biopsy performed on posttransplant day 30 (Fig 2). In response to the recognition of PyVAN, ciprofloxacin was introduced, and basic immunosuppression was modified by reducing the mycophenolate mofetil dose by 50% and implementing

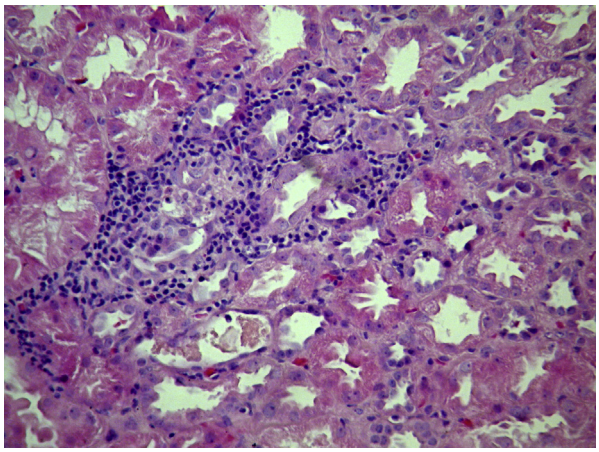

Fig 1. Focal tubulointerstitial inflammation. No intranuclear inclusions are seen in the tubular epithelium.

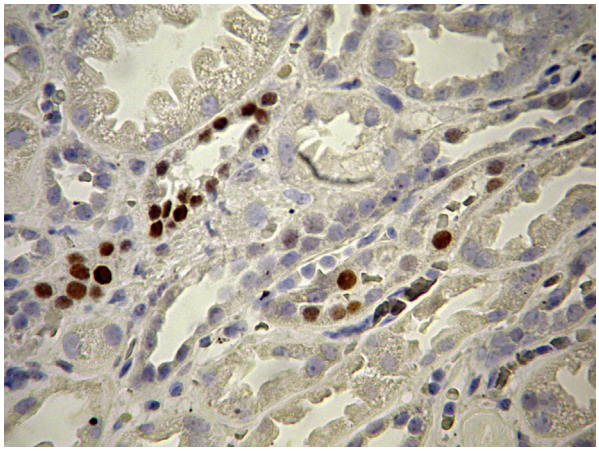

Fig 2. SV40 antigen is present in some of tubular epithelial cells (nuclear reaction).