

Polyoma Virus in Renal Transplant Recipients

Patricia D. Weiskittel



The human polyoma viruses belong to the papovavirus family. They were named BK and JC after the initials of the patients in whom they were identified in the 1970s. The BK virus was identified in a renal transplant recipient with ureteral stricture and the JC virus in a patient with Hodgkin's disease and progressive multifocal leukoencephalopathy (Binet, Nickeleit, & Hirsch, 2000). A third virus in this group is simian virus 40 (SV40), which has little pathologic significance in humans.

The documented worldwide rate of seroprevalance in adults is 60%-80% (Randhawa & Demetris, 2000). First infections usually occur in childhood (age 3-4 years) via the respiratory route, and the virus remains latent in the urogenital tract. The primary infection is generally asymptomatic, but when symptoms occur they are fever and a nonspecific upper respiratory infection (Reploeg, Storch, & Clifford, 2001). Reactivation and intermittent shedding of the virus can occur spontaneously in immunocompetent persons and frequently in those with altered cellular immunity as in pregnant women, cancer patients receiving chemotherapy, patients with human immunodeficiency syndrome, and organ transplant recipients. In the immunocompromised host, JC virus can cause progressive multifocal leukoencephalopathy. BK virus causes hemorrhagic cystitis in bone marrow transplant recipients. Reactivation of polyoma virus type BK is now recognized as one cause of severe renal allograft dysfunction and potential graft loss. It is estimated that 10%-60% of

immunosuppressed renal transplant recipients have reactivation of polyoma virus, which is accompanied by shedding of urothelial cells. Viral shedding is not consistently associated with renal dysfunction (Randhawa & Demetris, 2000). The reported prevalence of BK virus (BKV) in retrospective studies is 1.9%-4.5% in

renal transplant recipients with a graft loss exceeding 30% (Binet et al., 2000).

Diagnosis

Human polyoma virus-associated interstitial nephritis has been diagnosed in kidney and simultaneous kidney/pancreas transplant recipients

Infection and rejection have been the most critical complications following renal transplantation. Rejection rates have decreased recently with the advent of new and more powerful immunosuppressive agents. However, infection continues to be a serious complication. The use of broad-spectrum antibiotics and the development of antiviral agents have provided effective tools to combat the infectious processes traditionally seen in renal transplant recipients. Recently, a new viral illness has been identified in this population. Polyoma virus infection has been identified as the cause of allograft dysfunction and graft loss. This paper reviews the current prevalence and outcome of renal transplant patients infected with polyoma virus.

Goal:

Discuss the prevalence, diagnosis, clinical management, and outcome of polyoma virus infection in renal transplant recipients.

Objectives:

1. Cite the prevalence of polyoma virus infection in renal transplant recipients.
2. Identify the diagnostic techniques used to confirm the diagnosis of polyoma virus nephropathy.
3. Describe the outcome of polyoma virus nephropathy in renal transplant recipients.

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(Randhawa et al., 1999; Trofe et al., 2000). The clinical presentation is typically that of an increase in serum creatinine, prompting a kidney biopsy to rule out acute rejection or drug toxicity.

BKV can be detected in the urine, plasma, and biopsy tissue of patients. It is identified in the urine by the presence of cells containing viral inclusion bodies known as "decoy cells." This method, however, has limited capability to predict clinical disease because it has been found to be associated with BKV nephropathy in only 28% of cases (Randhawa & Demetris, 2000). Polymerase-chain reaction assays (PCR) for BKV DNA are performed on plasma. The PCR process is a molecular biology technique used to identify and amplify DNA of specific disorders such as Hepatitis C and retroviruses including human immunodeficiency syndrome (HIV) and cytomegalovirus (CMV). This technique has become an important tool clinically because it is able to detect specific DNA from even low numbers of pathogens present in plasma, urine, or tissue (Dudley, 1997). Nিকেleit, Klimkait, et al. (2000) performed PCR assays for BKV DNA on plasma samples from patients with histologically confirmed BKV nephropathy, a control group with no signs of BKV infection or viral shedding, and a group with asymptomatic shedding. The results of this study were a sensitivity of 100% and a positive predictive value of 85%, identifying PCR as a valuable clinical tool for the detection of BKV (Nিকেleit, Klinkait, et al., 2000).

In renal biopsy specimens, cells infected with BKV cause an infiltration of the tissue with mononuclear and polymorphonuclear cells and inflammation of the renal tubules that are very similar to the pattern seen with acute allograft rejection. The distinguishing change that establishes the diagnosis of BKV is the presence of viral inclusion cells in the biopsy specimen. However, it is difficult to distinguish between the effects of viral pathology on the tissue and the changes caused by acute rejection. Therefore, clear identification relies on more sophisticated immuno-

histochemical analysis or in situ hybridization (Randhawa & Demetris, 2000). Immunohistochemical analysis involves staining the tissue with an antibody of a related pathogen or virus. In the case of BKV, the related SV40 antibody will produce positive staining of the viral inclusion cells in the tissue sample. SV40 is not seen as a natural pathogen in man but has a 70% similarity to the human BK and JC viruses (Randhawa et al., 1999). In situ hybridization is a method used to localize the DNA of BKV within the cells of the renal tissue. This technique involves the use of a complimentary chemical probe to which the pathogen has affinity. The virus is attracted to the probe and forms a hybrid or crossbreed of the original virus. If hybridization does not occur, the tissue is negative for the offending virus.

Literature Review

The current literature identifies the number or series of cases diagnosed at various centers over the last 2-3 years. The number of reported cases ranged from 5 to 51. The reported prevalence rates were 2.5% (Howell et al., 1999), 4.5% (Nিকেleit, Hirsch, et al., 2000), 4.6% (Ramos, Drachenberg, Papadimitriou, Find, & Wali, 2001), 5.3% (Barri et al., 2001), and 7.1% (Binet et al., 2000).

The clinical features associated with polyoma virus in these series included lymphocele, bacterial urinary tract infection, hematuria, CMV infection (Howell et al., 1999), ureteric stricture (Howell et al., 1999; Randhawa et al., 1999), an acute rejection episode or recurrent acute rejections (Ahuja et al., 2001; Barri et al., 2001; Binet et al., 2000; Howell et al., 1999; Nিকেleit, Hirsch, et al., 2000; Randhawa et al., 1999), and calcineurin inhibitor toxicity (Randhawa et al., 1999). In all series reviewed, patients presented with a rise in serum creatinine prompting further investigations to identify the cause of the renal dysfunction.

Renal biopsy was part of the differential diagnosis regimen in all series, using either immunohistochemistry or in situ hybridization to

identify polyoma virus in the renal tissue. Plasma PCR was performed on patients in the series reported by Nিকেleit, Hirsch, et al. (2000); Ramos et al. (2001) and Randhawa et al. (1999). All series also performed urine cytology in an effort to identify the presence of "decoy" cells. A combination of the above-mentioned diagnostic tools was used to confirm the diagnosis of polyoma virus infection in the transplant kidney. Randhawa et al. (1999) reported two cases diagnosed as chronic rejection with the final diagnosis of polyoma virus infection made after examination of the nephrectomized kidney.

The immunosuppressive regimens used in these studies varied from center to center. Six of the seven patients in the Howell et al. (1999) study received cyclosporine, mycophenolate mofetil, and steroids. The seventh patient received cyclosporine, azathioprine, and steroids. One patient received induction therapy with OKT3®. Two patients in the series had early rejection episodes treated with methylprednisolone, one had additional therapy with OKT3, and one was switched from cyclosporine to tacrolimus. Twenty of the 22 cases reported by Randhawa et al. (1999) received tacrolimus-based immunosuppression and the other two cyclosporine. Fourteen cases were treated for rejection, two requiring OKT3 or antilymphocyte globulin administration. Seven of the nine cases reported by Nিকেleit, Klinkait, et al. (2000) received initial therapy with antilymphocyte globulin, cyclosporine, azathioprine, and methylprednisolone; one patient received the above regimen with mycophenolate mofetil instead of azathioprine; and one received the regimen with tacrolimus instead of cyclosporine. All nine patients suffered rejection episodes treated with methylprednisolone for 3 days and a polyclonal antilymphocyte preparation or OKT3 for 6 days. Of the 10 cases reported by Ahuja et al. (2001), eight received mycophenolate mofetil and tacrolimus-based immunosuppression, and the remaining two had

mycophenolate mofetil and cyclosporine-based regimen. The two cyclosporine patients were switched to tacrolimus prior to the diagnosis of polyoma virus infection. Seven of these cases had a prior diagnosis of acute rejection and received methylprednisolone with two receiving OKT3 or a polyclonal antilymphocyte preparation. At the time of diagnosis of polyoma virus, all 10 were diagnosed with concurrent acute rejection. Nine were treated with methylprednisolone with no response. One patient received a polyclonal preparation followed by OKT3. In the Ramos et al. (2001) series, 5 patients were on cyclosporine and 46 were on tacrolimus. All but one patient received mycophenolate mofetil. The eight cases reported by Barri et al. (2001) received induction therapy with either a polyclonal preparation or an IL-2 receptor blocker (basiliximab) and triple therapy with either tacrolimus or cyclosporine, prednisone, and mycophenolate mofetil. Seven in this series received tacrolimus-based immunosuppression. Six of the eight had a least one rejection episode prior to the diagnosis of polyoma virus.

Treatment

The consensus from this series is that the most effective treatment available at this time is the reduction or alteration of immunosuppressive therapy. This includes decreasing or stopping mycophenolate mofetil, reducing the dose of calcineurin inhibitor (cyclosporine or tacrolimus), or stopping the calcineurin inhibitor. Some of the studies also switched the patient from one calcineurin to the other in an attempt to improve renal function and clear the virus (Ahuja et al., 2001; Barri et al., 2001; Howell et al., 1999; Randhawa et al., 1999). The rationale for decreasing immunosuppression is to allow the host better clearance of the virus resulting in a decreased viral load. Improved host immunity is the only therapeutic approach available until effective antiviral therapy is developed.

There is no specific antiviral agent identified to treat polyoma virus nephropathy noted in the renal transplant literature. However, there are reports of successful treatment using cidofovir in the treatment of acute hemorrhagic cystitis due to polyoma virus after allogeneic bone marrow transplantation (Vianelli et al., 2000) and the treatment of progressive multifocal leukoencephalopathy caused by the JC virus (Segarra-Newnham & Vodolo, 2001). Cidofovir is a nucleotide analogue that inhibits viral DNA polymerase and is effective against human CMV infection. It has been shown to be effective against the human polyoma virus in vitro (Andrei, Snoeck, Vandeputte, & De Clercq, 1997). One of the major side effects of cidofovir is nephrotoxicity. Renal impairment is the major toxicity of this drug, and cases of acute renal failure requiring dialysis have occurred. Therapy with cidofovir is contraindicated in patients with a serum creatinine > 1.5 ng/dl or a calculated creatinine clearance < 55 ml/min (Gilead Sciences, 2000).

Prehydration is recommended prior to and following dosing. Monitoring of therapy includes serum creatinine and urinary protein excretion. This is probably the major reason that this drug has not been used for treatment in the renal transplant population with polyoma virus nephropathy who already have renal impairment from the virus.

Outcome

Graft loss has been high in all series. The percentages are 14% (Howell et al., 1999), 36% (Randhawa et al., 1999), 45% (Nickeleit, Hirsch, et al., 2000), 80% (Binet et al., 2000), 70% (Ahuja et al., 2001), 23.5% (Ramos et al., 2001), and 25% (Barri et al., 2001). The remaining patients have remained stable with decreased renal function.

Conclusions

Polyoma virus nephropathy is now a recognized cause of transplant renal dysfunction and allograft loss. This must now be added to the list of

differential diagnosis considered when a renal transplant patient presents with allograft dysfunction. There are now more precise diagnostic tests available to the clinician that delineate the changes seen from acute rejection. The immunosuppression regimens consisted of triple therapy with some receiving monoclonal antibody (OKT3) or polyclonal antilymphocyte agents. No one specific agent has been identified as the causative factor. The use of the combination of more powerful agents to prevent rejection has resulted in the reactivation of this virus leading to renal impairment. The treatment recommended by the authors reviewed for this article is a decrease in immunosuppression, even though this has been only marginally effective. The outcome for the allograft is dismal in the face of this disease. At this time there is not an antiviral agent specific to polyoma virus that does not cause significant renal toxicity.

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Posttest – 1.4 Contact Hours

Posttest Questions

(See posttest instructions on the answer form, next page)

- The documented worldwide rate of seroprevalance of human polyoma virus in adults is:**
 - 10%-30%.
 - 40%-60%.
 - 60%-80%.
 - 80%-100%.
- Primary infections of polyoma virus occur in childhood via the**
 - gastrointestinal tract.
 - respiratory tract.
 - urinary tract.
 - genital tract.
- Following primary infection, the virus remains latent in the**
 - respiratory tract.
 - spleen.
 - urogenital tract.
 - liver.
- Which clinical finding would cause you to suspect polyoma virus infection?**
 - Upper respiratory tract symptoms.
 - Elevated white blood count.
 - Gastrointestinal tract symptoms.
 - Elevated serum creatinine.
- You suspect a patient may have polyoma virus infection. Which test would provide for the greatest sensitivity and highest predictive value?**
 - Urinalysis to detect “decoy” cells.
 - PCR assays for the BK virus.
 - Serology testing for JC virus.
 - Renal biopsy.
- A patient expresses concern about the polyoma virus infection. You cite the prevalence reported in the literature of polyoma virus nephropathy in transplant recipients is between**
 - 2%-8%.
 - 2.5%-7.1%.
 - 3%-8%.
 - 3.5%-7.5%.
- The predictive rate of “decoy cells” in the urine for polyoma virus nephropathy is**
 - 50%.
 - 38%.
 - 28%.
 - 40%.
- A patient is receiving cidofovir for treatment of polyoma virus infection. You should assess the patient for**
 - nephrotoxicity.
 - metabolic alkalosis.
 - hepatotoxicity.
 - respiratory acidosis.
- What is the current approach to treatment of polyoma virus nephropathy?**
 - Monoclonal antibody therapy.
 - Increase immunosuppression.
 - Polyclonal antibody therapy.
 - Decrease immunosuppression.
- A patient with polyoma virus infection expresses concern about the loss of the kidney transplant. You explain the literature reports graft loss is between**
 - 14%-80%.
 - 25%-50%.
 - 36%-70%.
 - 23.5%-80%.

ANSWER FORM

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5. a b c d
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7. a b c d
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9. a b c d
10. a b c d

Goal:

Discuss the prevalence, diagnosis, clinical management, and outcome of polyoma virus infection in renal transplant recipients.

Evaluation	Strongly disagree		Strongly agree		
	1	2	3	4	5
1. The objectives were related to the goal.					
2. Objectives were met					
a. Cite the prevalence of polyoma virus infection in renal transplant recipients.	1	2	3	4	5
b. Identify the diagnostic techniques used to confirm the diagnosis of polyoma virus nephropathy.	1	2	3	4	5
c. Describe the outcome of polyoma virus nephropathy in renal transplant recipients.	1	2	3	4	5
3. The instructions were clear to complete this activity.	1	2	3	4	5
4. I would rate the learning level of this self-study as basic.	1	2	3	4	5
5. Minutes required to complete self-study, including the article and posttest:	_____ minutes				

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