BK Virus Interstitial Nephritis : Another Cause of Acute Graft Dysfunction

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Acute transplant rejection, drug toxicity and mechanical complications (ureteral obstruction, urine leak, renal artery stenosis) are the most common causes of acute renal allograft dysfunction. Less common causes of graft dysfunction include hypovolemia, ischemic nephropathy, recurrence of original kidney disease or systemic infection. However viral infections, such as polyomavirus induced interstititial nephritis have not been much appreciated as the cause of renal graft dysfunction. Although BK virus infection in organ transplant recipients is a rare complication, its incidence seems to be increasing.

Polyomavirus (PV) is a nonenveloped, double-stranded DNA virus. Two strains are associated with disease in humans — BK virus and JC virus. Even though 60-80% of adults are serologically positive, PV has no great clinical significance in immnocompetent individuals. Primary infection appears to occur in early childhood and is usually asymptomatic. In healthy individuals, PV resides in a latent state in the kidney and peripheral blood. Morphologic evidence of viral activation is the presence of PV infected cells in the urine (intranuclear inclusion cells; decoy cells). Asymptomatic PV viuria has been detected in approximately 3% of pregnant women, 10-45% of renal transplant recipients and 50% of bone marrow transplant patients. In immnocompromised patients, PV can cause an interstitial nephritis with cytopathic signs and renal failure. In addition, renal transplant patients were reported to suffer from BK virus associated ureteritis and ureteral stenosis and bone marrow transplant recipients from hemorrhagic cystitis. JC virus can cause multifocal leucoencephalopathy, mainly in AIDS patients.

PV interstitial nephritis is associated with focal or diffuse interstitial infiltration. Inflammatory infiltrates are predominantly composed of lymphocyte (T4 and T8) and histiocytes in combination with some PMNL and plasma cells. These findings mimic acute transplant rejection. However, tubulitis and intimitis, the characteristic features of acute transplant rejection, are not prominent. A more perplexing problem, however, is that PV interstitial nephritis may coexist with acute transplant rejection. The diagnostic hallmark on light microscopy is the detection of intranuclear viral inclusions, which are exclusively found in renal tubular epithelial cells. Cells with viral changes are often enlarged with polymorphic nuclei. By electron microscopy, intranuclear viral particls are granular, sometimes arranged as crystalloids. They measure between 35 and 40 nm in diameter, a size characteristic for PV. In the cytoplasm, viral particles are rarely noted by electron microscops. A definitive diagnosis of PV disease is made by EM examination of urinary sediments or tissue for viral particles, immnohistochemistry, or detection of viral nucleic acids by hybridization methods or the

polymerase chain reaction (PCR). JCV and BKV can be distinguished from each other only by immunohistochemical staining, in situ hybridization with DNA probes, or PCR.

Early reports, including a large study of BKV and JCV infection in 483 renal transplant patients suggested the absence of association between PV infection and poor clinical outcome (viral activation in 6% and graft dysfunction in 1%). More recent studies, however, describe PV interstitial nephritis and graft dysfunction that mimics acute transplant rejection, and its clinical course often ends with graft failure. Functional impairment of PV interstitial nephritis is caused by interstitial infiltration, tubular necrosis, rarely ureteral stenosis and possibly by coexisting transplant rejection. Total loss of graft fuction is often a result of withdrawal of immnosuppressive therapy and progression of transplant rejection PV disease, a potentially serious complication following organ transplantation can cause recipients' mortality as well as a graft failure. Currently, although there is no systematic data available, many investigators believe that there is increasing incidence of PV disease, presumably due to the introduction of new potent immunosuppressive drugs.

There is no known effective treatment for PV infection. Many empirical trials with antiviral agents, interferon and gamma globulin, have not shown any consistent beneficial effects. Most investigatiors strongly believe that PV infection is fueled by potent immunosuppressive therapy and that judicious lowering of immunosuppression, while carefully monitoring for acute rejection, provides the best currently available approach for successful management of patient and allograft. This is truly a challenge because there are no methods available for either quantitating viral load nor qualitatively determining whether the interstitial infiltrates seen in biopsy tissue are directed against virus of allograft.

REFERENCES

1) Nickeleit V, Hirsch H, Bint I, Gudat F, Prince O, Dalquen P, Thiel G, Mihatsch MJ. Polyomavirus infection of renal allograft recipients. From latent infection to manifest disease. *J Am Soc Nephrol* **10**:1080-1089, 1999
2) Leventhal B, Soave R, Mouradian J, Cheigh JS : Renal dysfunction and hyperglycemia in a renal transplant recipient. *Transpl Infect Dis* **1**:288-294, 1999