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Pathology of viral infection on renal allograft

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By reason of requisite use of immunosuppressive drugs in transplant recipients, viral infection has become one of the most common conditions that complicate these patients. The infections can be localized or systemically involved. Pathological change is caused by both the direct effect of the virion on the host cells as well as collateral immunologic responses. In renal transplant recipients, the diversity of the allograft changes associated with viral infections has been reported. The leading pathogens comprise: cytomegalovirus (CMV), polyomaviruses (PV), and hepatitis virus. The popular Epstein-Barr virus (EBV) is a representative of oncogenic virus that causes hematologic malignancy which is also common among transplant population. The source of pathogens include latent viruses to pathogens of community and hospital origin.

Keywords: *Viral infection, Renal allograft.*

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Objective : To demonstrate and describe pathological changes in allograft kidney those were found associated with viral infection.

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วิภาวี กิตติโกวิท. พยาธิสภาพจากการติดเชื้อไวรัสต่อไตที่ได้รับการปลูกถ่าย. จุฬาลงกรณ์เวชสาร 2546 ต.ค; 47(10): 667 - 86

เนื่องจากในปัจจุบันมีผู้ป่วยที่ได้รับการปลูกถ่ายอวัยวะมากขึ้นเรื่อย ๆ ไตเป็นอวัยวะหนึ่งที่มีการปลูกถ่ายมากที่สุด ผู้ป่วยที่ได้รับการปลูกถ่ายไตมักจะต้องได้รับยากดภูมิคุ้มกันเพื่อป้องกันการเกิดภาวะ rejection ทำให้มีความต้านทานต่อการติดเชื้อน้อยกว่าคนทั่วไป การติดเชื้อไวรัสเป็นภาวะแทรกซ้อนอย่างหนึ่งที่สำคัญที่มักเกิดขึ้น และบางครั้งทำให้เกิดพยาธิสภาพต่อไตที่ปลูกถ่ายทั้งโดยทางตรงและทางอ้อม ซึ่งส่วนหนึ่งของผู้ป่วยเหล่านี้ไตที่ปลูกถ่ายต้องสูญเสียการทำงานไปในระยะเวลาต่อมา การติดเชื้อไวรัสที่พบบ่อยได้แก่ Cytomegalovirus (CMV), Polyomavirus (BK type) และ Hepatitis virus (HBV และ HCV) นอกจากนี้ยังมี Epstein-Barr virus (EBV) ซึ่งมักทำให้เกิดมะเร็งต่อมน้ำเหลืองในผู้ป่วยที่ได้รับการปลูกถ่ายอวัยวะได้บ่อย ๆ บทความนี้ได้รวบรวมการเปลี่ยนแปลงทางพยาธิสภาพในไตที่ปลูกถ่าย ซึ่งมีความเกี่ยวข้องกับการติดเชื้อไวรัส แต่ไม่รวมถึงพยาธิสภาพในภาวะ rejection ที่อาจเกิดตามหลัง หรือจากการชักนำโดยการติดเชื้อไวรัส

Since renal transplantation enables recipients to regain their essential functions in life and uncomplicated way of living, it has become a popular procedure worldwide for years. However, not all of these patients are satisfied with the result. Many developed complications leading to graft failure. In addition to graft rejection, which is the most common complication cited, viral infection is also popular that it can give rise to graft loss.

Viral infection and renal allograft: Pathology and pathogenesis

Approach to pathological changes associated with viral infection in allograft sometimes needs focusing on each anatomical and histological component of the kidney, i.e. glomeruli, interstitium, renal tubules, and blood vessels as listed in Table 1. Occasionally, the ureter is involved and causes obstructive uropathy leading to allograft dysfunction.[1-3]

Glomeruli

Changes that occur in glomerulus, according to viral infection, can be resulted from the direct effect of the pathogen on the glomerular components or a consequence of immune reaction through the process of graft rejection or immune complex formation. These pathological changes can be described as follows:

Acute glomerulonephritis

Acute CMV glomerulonephritis

Rare acute glomerulonephritis caused by viral infection has been documented. The pathogens are demonstrable by viral inclusions in infected cells such as cytomegaloviral intranuclear inclusions. [4] The pathological changes in renal biopsy show intranuclear inclusions in the enlarged endothelial cells with marked infiltrate of mononuclear inflammatory cells and polymorphs. Focal necrosis and crescent formation are encountered. [5] The surrounding interstitium of

Table 1. A list of viral-associated pathological changes in renal allograft.

Non-neoplastic viral-associated pathological changes in renal allograft**
Glomeruli
Direct infection
Acute glomerulonephritis (e.g. CMV)
Indirect consequence
Membranoproliferative glomerulonephritis (type I and III)
Membranous glomerulopathy
C1q glomerulopathy
Immunotactoid glomerulopathy
Collapsing glomerulosclerosis
CMV –associated glomerulopathy
Tubules and interstitium
Tubulointerstitial nephritis*
Viral-associated neoplasm of the renal allograft
Post-transplant lymphoproliferative disorder (PTLD)

**Not include viral-associated allograft rejection

*Exclusion from acute allograft rejection is always problematic.

the infected glomeruli also displays mononuclear inflammatory cell accumulation. Rare viral cytopathic change is observed in the interstitium and tubules. No specific staining pattern is found in immunofluorescent studies. Ultrastructural examination reveals endothelial cell damage and reduplication of capillary basement membrane without electron-dense deposit. Detection of CMV is confirmed by electron microscopy and *in situ* hybridization. The reported case was found to associate with the CMV seronegative recipient who received a kidney from a seropositive donor. The course was started 5 months after transplantation, the patient developed renal insufficiency and proteinuria. There was a rejection episode on day 45 that responded to OKT3. After being treated with 2-month course of gancyclovir, the glomeruli returned to normal in the follow-up biopsy. [6]

Membranoproliferative glomerulonephritis (MPGN)

Many renal transplant recipients who experienced HCV and HBV infection developed deterioration of glomerular function. The common pathological change of the kidney among these patients is membranoproliferative glomerulonephritis. This lesion is present as a renal complication of hepatitis B and/or hepatitis C antigenemia. [7] These patients usually present with severe proteinuria or nephritic syndrome and microscopic hematuria. Hypertension and renal failure are found in less number. Levels of serum complement are usually depressed, with demonstrable HBsAg, antibody to hepatitis core antigen, and circulating immune complex. The pathology of the altered glomeruli comprises MPGN type I or occasionally type III.

In type I MPGN, the glomeruli show uniform changes. They are enlarged and the glomerular cellularity is diffusely increased in all segments of the glomerular tufts. This results in prominent glomerular lobulation. The increased cellularity partly resulted from monocytes and lymphocytic infiltrate, influx of polymorphonuclear granulocytes can be seen in early period [8], together with demonstration of C3 deposition. The glomerular capillary walls are thickened and can be irregular. Splitting of the glomerular basement membrane is demonstrable in Periodic acid-Schiff (PAS) and silver methenamine stains in the thickening part of the capillary loops. It often shows two or more layers of basement membrane, which is stained positive by PAS or silver separated by a ›agyrophilic region. This is also described as "tram tracking" or duplication of the glomerular basement membrane. Immunofluorescence demonstrated mainly IgM and C3 deposition in the mesangial area and along the peripheral capillary walls. [7,9] HBsAg is demonstrated in the mesangial area by immunofluorescence in some cases. [10] Subendothelial and/or mesangial deposits are observed under electron microscopy.

The pathogenesis of this condition is the trapping of circulating immune complexes that are composed of HBV antigens and localized to the mesangium and subendothelium regions in glomeruli as a result of passive trapping of immune complex formation.

Membranous glomerulonephritis

Some cases of *de novo* membranous glomerulonephritis occur in renal allograft recipients with HCV seropositive. The incidence among these HCV infection recipients is as high as 3.66 % in 24 months after transplantation. [11] These patients can have only asymptomatic proteinuria to proteinuria of nephrotic range and/or microscopic hematuria with or without mild renal insufficiency.

The pathological features of the glomeruli have no difference from the primary membranous glomerulonephritis that occurs in the native kidney. No endocapillary proliferation is encountered. The glomeruli are diffusely affected showing widely patent capillaries with uniform capillary loops thickening. Fluorescent antibody studies reveal diffuse granular deposits of IgG and variable C3 along the glomerular capillary loops. Electron microscopy confirms the diagnosis by demonstration of subepithelial electron-dense deposits.

These cases showed negative antinuclear antibodies, cryoglobulins, normal complement, and negative rheumatoid factors. Neither the HCV antigen nor the specific antibody has been captured. The pathogenesis of this lesion is deliberative.

Administration of interferon that resulted in clearance of virus and lessened proteinuria. High dose steroid administration helps to reduce protein excretion in some patients. In long-term course, most of the patients develop progressive worsening of renal function, with increased serum creatinine and persistent proteinuria that ends up with graft failure.

C1q glomerulopathy

A case of *de novo* C1q nephropathy that occurred in a kidney pancreas transplant recipient with simultaneous polyomavirus interstitial nephritis has been reported. The diagnosis was made by detection of C1q deposits in electron microscopy and by immunofluorescence study. The interstitium which showed leukocytic infiltrate was initially interpreted as acute cellular rejection. BK virus tubulointerstitial nephritis mimicking rejection was proposed in the second biopsy after failure of rejection treatment. The diagnosis was confirmed by blood and urine PCR study for BK virus. The author proposed that C1q nephropathy was induced by BK virus. [12]

Immunotactoid glomerulopathy

A case of *de novo* immunotactoid glomerulopathy was found in one renal allograft recipient with CMV infection. The patient presented with hematuria, proteinuria and acute renal failure 2 weeks following an acute rejection episode that was treated with high dose immunosuppression. The symptom developed 6 weeks after cadaveric renal transplantation. At the same period, CMV viremia with acute hepatitis and bone marrow suppression were detected. The viral syndrome subsided after the withdrawal of immunosuppression and the administration of gancyclovir. The patient remained diseases free within twenty months of follow-up.

The pathological findings were the presence of dense eosinophilic deposits occluding the capillary lumens diffusely, mild interstitial edema without inflammation or hemorrhage, and focal tubular atrophy. No occlusion or endothelial swelling in small blood vessels. Stains for amyloid were negative. There was granular deposition of IgG, IgM, and C3 along the glomerular capillary walls and lumens in fluorescent antibody studies. Ultrastructural examination revealed large electron-dense fibrillar deposits within the subendothelial space and focally in the mesangium, which was correlated with the immunofluorescence findings. The fibrillary material was densely packed cylindrical microtubules that measured 31 to 43 nm in diameter.

The presence and disappearance of the lesion at the same time with CMV viremia suggests that

these two conditions were temporally linked, though no direct evidence of direct relations was demonstrable. The exact pathogenesis of the disease remains unknown. [13]

Collapsing glomerulosclerosis

Addition to the rare de novo collapsing glomerulopathy [14], this type of glomerular change has been reported with the association of parvovirus B19 infection. [15]

The pathological change of the lesion is characterized by diffuse or focal, global or segmental collapses of glomerular capillaries, swelling and proliferation of podocytes filling the Bowman's space, hyaline arteriosclerosis, tubular epithelial degenerative changes, microcystic dilatation of tubules and interstitial inflammatory cell infiltrate and fibrosis. [16,17]

The lesion was found associated with human immunodeficiency virus (HIV) and parvovirus B 19 infection. The possible pathogenesis of this lesion is injury of the visceral epithelial cells leading to cell cycle dysregulation and proliferation. The disorder is more common among blacks with a high incidence of nephrotic syndrome and rapidly progressive renal failure that often leads to graft loss. The lesion was classified as an aggressive form of focal segmental glomerulosderosis (FSGS). Another possibility of the pathogenesis of collapsing glomerulopathy among renal transplant recipients without viral complicated condition is hemodynamic disturbance. [16]

Treatment with intravenous immunoglobulin (IVIG) gives a satisfactory result in some cases. In patients who received an intense immunosuppression, the outcomes were not impressive, the disease progressed and ended up with graft failure as usually seen in *de novo* condition. [15] Aggressive blood pressure control is an important part of the treatment.

CMV-associated glomerulopathy

The pathological feature of this entity was first described by Richardson *et al.* [18] The lesion was found in renal transplant recipients with CMV viremia.

Glomerular changes in this lesion comprise diffuse endothelial hypertrophy and necrosis, narrowing or obliteration of capillary lumens, fine fibrillar webs of PAS-positive material deposition in glomerular capillaries, mild segmental hypercellularity, and mononuclear cell infiltration without tubular changes. Immunofluorescent studies revealed deposition of IgG. IgM, and C3 along the glomerular capillary basement membrane and within the mesangium. Anti-CMV antibody staining was observed within glomerular capillaries. No viral inclusion was demonstrated by electron microscopy.[18] Later Herrera *et al.* described a similar lesion but without anti-CMV antibody deposition in immunofluorescent studies and no viral particle was detected by electron microscopy. The author suggested that the lesion is probably represented for acute transplant glomerulopathy resulting from antiendothelial antibody injury as a protracted, early, or unresolved form of acute vascular rejection. [19] There was a high proportion of CD8+ T lymphocytes founded by Tauzon *et al.* among the mononuclear inflammatory cells that infiltrate the glomeruli.[20] These cells expressed Class II major histocompatability complex (MHC) antigens (HLA-DR), which van Es et al. found that there was a relation between CMV infection and Class II MHC antigen upregulation on CD8+ lymphocytes. [21]

Tubules and interstitium

Tubulointerstitial nephritis

Since the renal tubular cells are the most vulnerable to viral infection, most of the viruses attack tubular epithelium. There is no difference of the interstitial reaction among various kinds of viruses that infect the allograft. Even acute rejection process is indistinguishable. The only hallmarks that can be a clue for discrimination of each virus is the tubular cytopathic change, although some exceptional cases of overlapping exist. [22] Immunohistochemical study or detection of viral DNA is needed for confirmation.

CMV nephritis

To diagnose CMV nephritis, the classical cytopathic change should be documented, otherwise immunohistochemical staining for viral protein such as CMV early nuclear protein (CMV-A) [23] or CMV DNA [24] must be positive on the suspicious cells. The classical CMV cytopathic change is characterized by enlargement of the infected cells bearing atypical large nuclei containing basophilic inclusion surrounded by a halo — Cowdry type A inclusion, and intracytoplasmic inclusion. The infected cells include glomerular capillary and peritubular capillary endothelial cells, interstitial inflammatory cells, tubular epithelial cells, and glomerular epithelial cells. Variable degree of interstitial infiltration of mononuclear inflammatory cells, tubular atrophy and interstitial fibrosis can be detected. Prominent arteriolar endothelial cells are evident in some cases. [24]

Herpes simplex virus interstitial nephritis

Herpes simplex virus infection is commonly present in general population as a mucosal lesion. Disseminated infection or interstitial nephritis is extremely rare and only occurs in immunodeficient host, especially the latter condition, which found exclusively among renal allograft recipients. The allograft is the foremost potential source of the viral infection. [25]

The lesion is characterized by patchy necrosis with acute inflammatory cell infiltration, nuclear fragmentation and hemorrhage. Tubular epithelial cells in this inflamed area display chromatin clearing and margination, intranuclear inclusions, and occasional multinucleate cells. Outside this active lesion, milder degree of interstitial infiltrate of mononuclear inflammatory cells can be found. However, the lesion is strongly suggestive for herpes virus infection, it can be confirmed by immunohistochemical staining for herpes simplex virus type 1 and 2. [26]

Polyomavirus nephritis

Polyoma virus nephritis in renal allograft recipients has become popular for 10 years. After Gardner *et al.* reported a new strain, BK— virus in the family of human papovavirus found in his Sudanese patient named BK, studies on the virus have started worldwide. [27] Other polyomavirus associated allograft nephropathy such as JC virus (JCV) and Simian virus 40 (SV40) were also found but less common.[28] Randhawa P. *et al.* found JCV DNA in needle biopsy specimen up to 36.8 % in cases with viral nephropathy.[29]

The most reliable diagnosis of polyoma BKvirus nephritis can be made histologically in a graft biopsy. Enlarged infected cells that exclusively involve tubular epithelium characterize BK polyoma-

virus interstitial nephritis. These cells exhibit nuclear enlargement and atypia bearing viral inclusions. Nickeleit *et al.* has described four different variants of intranuclear inclusion bodies. Type 1 is an amorphous basophilic ground-glass variant, which is found most common. Type 2 is described as an eosinophilic granular type surrounded by a halo. Type 3 is a finely granular form lacking a halo. Type 4, the least considered for BKV, is a vesicular variant with markedly enlarged nuclei and clumped, irregular chromatin. The last type might be mistaken as neoplastic change. These infected cells are usually extruded from the epithelial cell layer into tubular lumens. Although cytopathic changes can be found along the entire nephron, they are most abundant in collecting ducts and distal tubular segment. [30]

The surrounding interstitium shows wide range of inflammatory cell infiltrate associated with tubulitis that plasma cells might be predominating. It can give a histological appearance similar to both vascular and cellular rejection that can be successfully treated by tapering immunosuppression. [31]

Drachenberg *et al.* described morphological spectrum of polyomavirus nephritis in three categories: mild, moderate and severe, and advanced. The lesion that shows viral cytopathic changes without or minimal inflammation of isolated tubules would be classified as mild. The moderate degree is applied when there is a cytopathic change associated with patchy tubulointerstitial inflammation and atrophy, and the severe grade comprises cytopathic changes with diffuse inflammatory cell infiltrate. The last category, advanced lesion is applied when the biopsy shows graft sclerosis with rare or absent viral cytopathic changes, indistinguishable from chronic allograft nephropathy. There is progression of the lesion from mild to moderate or severe disease. The mean time of diagnosis is not much different among the mild, moderate, or severe categories, 1.05 to 1.3 years after transplantation. [32] There is difference of the cell infiltrate in polyoma virus nephritis compared with acute rejection. Immunostaining for T and B cells in polyomavirus nephritis revealed marked increase of B cells (CD20) and reduced cytotoxic T cells. [33]

Electron microscopy demonstrates intranuclear paracrystalline arrays of non-enveloped non-capsid viral particles 35-38 nm in diameter. [34]

The viral inclusion bodies can also be found in the superficial layer of transitional epithelium of the renal pelvis and ureter that can cause ureteritis and stenosis leading to obstructive uropathy and rapid deterioration of the allograft function.

Adenovirus nephritis

Adenovirus infection in renal allograft usually presents as necrotizing hemorrhagic tubulointerstitial nephritis. The changes sometimes lead to renal failure. The patients usually present with dysuria and macroscopic hematuria, which might be resulted from viral-associated hemorrhagic cystitis.

The morphologic feature is characterized by patchy or diffuse inflammatory cell infiltrate associated with edema and small foci of hemorrhage. The inflammatory cells include lymphocytes, macrophages, plasma cells, and scattered polymorphonuclear leukocytes. Granuloma formation can be found associated with ruptured tubules. The tubular epithelial cells are enlarged with smudgy intranuclear viral inclusions, which can be observed in urine cytology. [35,36]

Immunohistochemical staining for adenovirus antigen in the cytoplasm and nuclei of the affected cells is needed for confirmation, and exclusion of other pathogens that can give rise to the similar cytopathic changes e.g. polyoma virus and cytomegalovirus should be performed. [36]

Post-transplant lymphoproliferative disorder (PTLD)

The incidence of Epstein-Barr virus (EBV)-associated posttransplant lymphoproliferative disorder occurs in about 1 % of renal transplant recipients, varying from 0.7 to 2.4 % among adults and up to 4.5 % for children with the median time of diagnosis at 268 days. About 60 % was diagnosed within the first year. [37,38] Clinically, the lesion encompasses from transient lymphoid hyperplasia to aggressive B-cell malignancies.Renal allograft involvement is present in 10 to 36 % of cases. [39,40] The patients usually present with graft dysfunction and major proportion had episodes of significant rejection.

Histopathologic findings of PTLD lesions are classified into monomorphous and polymorphous patterns. The lesion is characterized by patchy confluent to nodular aggregates of immature lymphoid cells with presence of irregular areas of coagulative or liquefaction necrosis. There is a perivascular rim of viable lymphoid cells in the areas of necrosis in some cases. In polymorphous pattern, the infiltrative neoplastic cells are composed of a polymorphic mixture of immunoblasts, large cleaved and noncleaved cells, small round lymphocytes and plasma cells. The monomorphous lesion is composed of invariable large noncleaved cells and immunoblasts. The tumor cells usually infiltrate venous channels and damage the entrapped tubular epithelial cells. Extension to hilar fat and ureteric wall is not uncommon. Perineural and intraneural invasions are occasionally present. Large to medium-sized arteries are relatively spared. Areas away from obvious PTLD showed diffuse infiltrates of activated mononuclear cells without areas of serpiginous necrosis and atypical cells. The lesion is separated from changes found in chronic vascular rejection with intimal foam cell deposition that is associated with intense lymphoid hyperplasia and prominent germinal center formation without nuclear atypia and necrosis. EBV cannot be demonstrated in the latter.

Immunohistochemical staining for evaluation of expression of kappa and lambda light chain is required for evaluation of tumor cell clonality, as well as phenotypic study of B or T cell.

PTLD usually arises in the setting of refractory rejection that intense immunosuppression is applied. Early recognition of the lesion is critical for appropriate management. Possible risk factors associated with development of PTLD are the high level of immunosuppressive agents and status of EBV seronegative at the time of transplantation. [41] Another study by Shahinian VB et al found late-onset PTLD (>1 year posttransplant) up to 80 %. The only significant risk was EBV-negative serologic status at transplant. [42]

The allograft is one of the most common sites of PTLD occurrence. [37] Usually, the patients present with renal dysfunction. Ultrasound examination reveals a hilar mass with hydronephrosis and stenosis of renal vessels. [38] The other sites include tonsils, cervical lymph nodes, gastrointestinal tract, liver, oropharynx, hypopharynx, central nervous system, skin and

mucosa.[44]

Most of the PTLD are predominantly B-cell, whereas a T-cell origin is rarely observed.[44,45] But the extremely exceptional entity, natural killer (NK)/T-cell origin has also been reported.[46] Recently, the proportion of EBV-negative PTLD has increased. Human herpesvirus-8 might play certain roles in some of these patients.[47]

The optimal approach to treatment is largely unknown. Methods of treatment comprise reduction of immunosuppression, antiviral therapy, anti-CD20, chemotherapy, and local radiotherapy.[44]

Viral infection and renal allograft:general consideration

Polyomavirus

BK virus (polyomavirus hominis 1, BKV) is found up to 90 % of general population but rarely manifests as a disease except in those who have an impairment of immune function. Hemorrhagic cystitis, ureteric stenosis, vasculopathy, pneumonitis, encephalitis, retinitis, tubulointerstitial nephritis and multi-organ failure are the reported clinical manifestations associated with the presence of virus among those immunocompromised individuals.[48] Five to 7 %[49-51] of renal transplant recipients developed BK virus nephropathy at 6 to 150 weeks, averages 40 weeks, post-transplantation.[49] Not all the patients with BK viruria and viremia had BKV nephropathy. A study by Hirsch *et al.* revealed that BK viruria was found in 29.5 % of renal transplanted recipients at a median of 16 weeks posttransplantation (ranged 2 to 69), BK viremia 12.8 % at a median of 23 weeks (ranged 4 to 73), and 6.4-7 % of BKV nephropathy at a median of 28 weeks (ranged 8 to 86).[50]

Incidence of BKV viruria among pediatric kidney allograft recipients was 26 of 100 patients, while BKV viremia was found in only 5 patients. Two related factors for predictive of active BKV infection were negative antibody to BKV status of the recipients and presence of mycophenolate mofetil in baseline immunosuppression.[52] Reactivation of PV in native kidneys and urinary tract of pancreas transplant recipients is not uncommon (4 out of 38 patients) but does not cause significant renal function impairment.[53]

Risk factors for BKV nephropathy may include treatment of rejection episodes and increasing viral replication under potent immunosuppressive drugs, such as tacrolimus, sirolimus or mycophenolate.[33,49,54] The incidence of PV nephritis was also higher in cadaver donor transplants (2.6 % compared with 0.7 % in living donors), kidney-pancreas transplant, in males, and in diabetic patients.[55]

Urine cytology is a useful non-invasive screening test for evaluates renal transplant patients with polyomavirus reactivation. The positive predictive value of positive urine is found as high as 90 % and negative predictive value of the negative urine is 99 % and the accuracy of the test is 97 %. The number of polyomavirus infected cells in urine, decoy cells, has a strong correlation with the concurrent biopsies.[32] Protocol or surveillance biopsy is claimed to be helpful in the diagnosis of subclinical polyoma virus infection as well as subclinical rejection and chronic allograft nephropathy. Early or subclinical detection and treatment of polyomavirus-associated nephropathy results in lesser degree of interstitial fibrosis and lower baseline and subsequent serum creatinine.[56,57]

Quantitative PCR for BKV in the allograft tissue can be used for the prediction of patient at risk for BK virus nephropathy before presence of histological changes. [58] Another noninvasive diagnostic method for BK virus nephritis is proposed by measurement of BKV VP1 mRNA in urinary cells. The measure is claimed to be an accurate means with 93.8 % and 93.9 % of sensitivity and specificity (with the use of a cutoff value of 6.5x10BKV VP1 mRNA copy number per nanogram of total RNA). [59]

The mean time of histological diagnosis of BKAN is 14.4 months after transplantation (1.2-53 months). The incidence rose from 1 % in 1997 to 5.8 % in 2001 at the University of Maryland which one-third had lost graft function. The diagnosis of BKAN was based on demonstration of viral cytopathic change in renal biopsy tissue and urine cytology together with quantitative viral load in plasma with a threshold of >10,000 copies of BKV per ml of plasma. The course of BKAN after the reduction of immunosuppression follows one of the 2 pathways:

1) Clearance of the infection and disappearance of the viral cytopathic changes in biopsies and urine (20 %);

2) Persistence of viral replication associated with continuous tubular damage (70 %).

The rate of conversion from positive to negative urine cytology after the reduction of immunosuppression is higher in early detected cases. [60]

The quantitative PCR for BKV in urine can be used in following the course of infection in renal transplant patients which is claimed to be a sensitive and reliable method. [61]

Reduction in immunosuppression alone in the early course of the disease could stabililize the renal function, though some degree of allograft dysfunction existed. [62] Even multiple antiviral treatment regimens were added, failed graft occurred in up to 60 % of cases that dialysis was required. [55] The greater rate of graft failure following BKV nephritis was found among the renal transplant recipients who received antilymphocyte agent (OKT3/ATGAM) for presumptive acute rejection. [63] Graft failure occurs after four months of diagnosis of PV nephritis. [33]

CMV

CMV infection and CMV disease are common complication among renal transplant recipients. Most of the cases occur within 6 months after transplantation. Rare cases of late-onset CMV nephritis have been reported. Inflammation, stress mediators and some drugs might activate the virus by using distinct intracellular pathways. [64]

CMV DNA is found in inflammatory cells, tubular epithelium, and capillary endothelium in acute infection. During the latent period with persistent CMV in the graft, there is mild to moderate chronic changes in the graft. At this setting, CMV DNA is found in inflammatory cells, tubular and glomerular cells, and endothelial cells of the arterioles. [65] The cellular immune response in primary CMV infection needs CMV-specific CD8 T cells for elimination of the virus in the state of high viremia, while later on during persistent infection, CD4 T cells dominate the immune response for contribution of antiviral immunity. [66]

CMV glomerular vasculopathy is another pathological change that can be found in renal allograft. The lesion also causes deterioration of the allograft function. [67] Recently, CMV ureteritis in renal transplant recipients has been reported. The clinical presentation

of these cases is obstructive uropathy with absence of systemic illness, but it can also mimic allograft rejection with minimal obstructive symptoms.[68]

In patients with moderate immune deficiency such as long-term transplant patients on low-dose immunosuppression virus spreading is controlled but the eradication of cells harboring the active virus may be insufficient. Persistent CMV antigenemia may induce chronic inflammatory processes leading to allograft injury. [64] Despite of adequate treatment in that late CMV nephritis with gancyclovir and eradication of the pathogen, progressive graft dysfunction still occurred. [69]

VZV

Disseminated varicella zoster virus infection among renal allograft recipients is not uncommon. It can happen as a primary infection in majority or reactivation with dissemination forms. The main complications were hepatitis, pneumonitis, and disseminate intravascular coagulation that might involve the allograft kidney. The overall mortality rate is as high as 34 %. [70] The infection can be successfully treated with early administration of high-dose acyclovir combined with reduction of immunosuppression. [70,71]

HCV

Posttransplant de novo glomerulonephritis in HCV-positive renal allograft is not uncommon. The common types of lesion, which can be demonstrated in renal biopsy, preclude membrano-proliferative glomerulonephritis (type I and type III) and membranous glomerulopathy. [72] Patients usually have proteinuria and/or microscopic hematuria. The incidence is found up to 19-63.6 % [72,73] among the HCV-positive allograft recipients. Cruzado JM et al. study found that pretransplant interferon administration reduces the occurrence of posttransplant HCV-related de novo glomerulonephritis. [73]

The patients with HCV seropositive had a higher rate of retransplantation as well as a slightly low 7-year survival rate compared to the seronegative group. [74] By multivariate analysis, HCV-positive serology is one of the independent predictors of graft loss. [72]

Kamar et al. found that there was a significant increase of HCV viremia after transplantation, which did not differ significantly between the recipients who developed *de novo* glomerulonephritis and the ones without glomerular disease. The study also found that the viral diversity, complexity, and the proportion of nonsynonymous substitution per nonsynonymous site were significantly higher among the patients who developed glomerulonephritis after transplantation while at time of transplantation there was no difference of these factors. The findings suggest that occurrence of *de novo* HCV associated glomerulonephritis is not a direct effect of HCV on the renal cells but related to a higher immune response and/or particular cytokine production. [43]

Human herpes virus-8 (HHV-8)

HHV-8 is a novel gamma herpes virus detected in all forms of Kaposi's sarcoma, including posttransplant Kaposi sarcoma. Moreover, Castleman disease, PTLD, and primary effusion lymphoma are found in immunodeficeint hosts with HHV-8-seropositive. [47]

Adenovirus

Adenovirus infection is another uncommon disorder that complicates renal allograft. The outstanding manifestation is gross hematuria, which the correlated pathology includes hemorrhagic cystitis and necrotizing hemorrhagic tubulointerstitial nephritis, which can lead to renal failure. The clue for diagnosis in the renal biopsy is presence of glassy-appearing nuclear smudging or ground glass-like intranuclear viral inclusions with more extensive tubular necrosis and less extensive interstitial infiltrate in opposed to allograft rejection. Granulomatous interstitial nephritis also has been reported. [75] The altered cells can be detected in urine cytology as viral inclusion-bearing epithelial cells, but further investigation for confirmation either by immunohistochemical study or electron microscopic analysis is needed because these cells can mimic Decoy cells in polyomavirus infection.[22]

Table 2. Viruses and pathological changes in renal allograft and clinical manifestation.

Virus	Frequency	Clinical manifestation	Pathological changes
HSV-I, II*	Uncommon	Acute nephritis, deterioration of renal function	Necrotizing hemorrhagic TIN**
VZV*	Rare	Deterioration of renal function	DIC**
EBV*	Occasional	Deterioration of renal function, mass lesion, paraneoplastic syndrome	PTLD**
CMV*	Most common	Acute nephritis, deterioration of renal function	Acute CMV glomerulonephritis, TIN, Immunotactoid glomerulonephritis
HHV-8*	Rare	Deterioration of renal function, mass lesion, paraneoplastic syndrome	PTLD, Kaposi sarcoma
Adenovirus	Uncommon	Gross hematuria, acute nephritis, deterioration of renal function	Hemorrhagic cystitis, Necrotizing hemorrhagic TIN
Polyoma	Common (among western)	Hematuria, deterioration of renal function	Hemorrhagic cystitis, TIN, C1q glomerulopathy
HBV*	Common	Proteinuria, urine sediments, nephrotic syndrome	MPGN**, MGN**
HCV*	Common	Proteinuria, urine sediments, nephrotic syndrome	MPGN, MGN
Parvovirus B19	Rare	Nephrotic syndrome, rapidly progressive renal failure	Collapsing glomerulopathy

* HSV=Herpes simplex virus, VZV=Varicella zoster virus, EBV=Epstein-Barr virus, CMV= Cytomegalovirus, HHV=Human Herpes virus, HBV=Hepatitis B virus, HCV=Hepatitis C virus

**TIN=tubulointerstitial nephritis, DIC=disseminated intravascular coagulation, PTLD=post-transplant lymphoproliferative disorders, MPGN=membranoproliferative glomerulonephritis, MGN= membranous glomerulopathy

Parvovirus B19

Parvovirus B19 is a non-enveloped single-stranded DNA virus that commonly causes a benign childhood infection typically manifesting as a slapped-cheek rash. Among immunodeficient hosts, persistent anemia, occasional pancytopenia and collapsing glomerulopathy [76] can occur in the infected patients. In one reported case, the patient developed fever, polyarthralgia and pancytopenia with allograft dysfunction after eight weeks of transplantation. There was an elevated IgM titer against parvovirus B19. The renal biopsy showed no evidence of acute rejection but with moderate degree of tubular damage and parvovirus B19 viral DNA was detected in the renal tissue by PCR. After 10-day course of intravenous immunoglobulin (400mg/kg/day), the allograft function was improved to baseline with normalized blood count. These cases are donor transmitted primary infection. [77]

Viral infection and renal allograft: Conclusion

Diversity of viruses and their effects on renal allograft with associated clinical presentation or syndrome are summarized in Table 2.

There is difference in risk to expose to each virus and develop infection at the different time course after transplantation. Differential diagnosis can be narrowed by correlation of the history of time course, patients' status, and given immunosuppressive agents.

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กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งแพทยสภา (ศนพ.) จากการอ่านบทความเรื่อง **"พยาธิสภาพจากการติดเชื้อไวรัสต่อไตที่ได้รับการปลูกถ่าย"** โดยตอบคำถามข้างล่างนี้ ที่ท่านคิดว่าถูกต้องโดยใช้แบบฟอร์มคำตอบท้ายคำถาม โดยสามารถตรวจ จำนวนเครดิตได้จาก http://www.ccme.or.th

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คำถาม - คำตอบ

1. The pathological change in renal allograft associated with HCV infection is...
    a. Acute necrotizing glomerulonephritis
    b. Membranoproliferative glomerulonephritis
    c. Immunotactoid glomerulonephritis
    d. Collapsing glomerulosclerosis
    e. All of the above
2. Which of the following virus is usually found associated with hematologic malignancy arising in renal transplant recipients?
    a. Cytomegalovirus
    b. Polyomavirus
    c. HBV
    d. Epstein-Barr virus
    e. Parvovirus B19
3. Which of the follow is the risk factor for developing viral infection in transplant recipients?
    a. Negative serologic status in recipients and positive status in donor at time of transplantation
    b. The potent immunosuppressive regimen given to the recipient
    c. Cadaveric allograft
    d. Administration of antilymphocyte antibody
    e. All of the above

คำตอบ สำหรับบทความเรื่อง **"พยาธิสภาพจากการติดเชื้อไวรัสต่อไตที่ได้รับการปลูกถ่าย"**
จุฬาลงกรณ์เวชสาร ปีที่ 47 ฉบับที่ 10 เดือนตุลาคม พ.ศ. 2546
รหัสสื่อการศึกษาต่อเนื่อง 3-23-201-9010/0310-(1043)

ชื่อ - นามสกุลผู้ขอ CME credit ..... เลขที่ใบประกอบวิชาชีพเวชกรรม.....
ที่อยู่.....

1. (a) (b) (c) (d) (e)
2. (a) (b) (c) (d) (e)
3. (a) (b) (c) (d) (e)
4. (a) (b) (c) (d) (e)
5. (a) (b) (c) (d) (e)

4. The definite diagnosis for BK polyomavirus nephritis can be made by...
    a. Quantitative PCR for BKV in the allograft tissue
    b. Histologic detection of BK virus cytopathic change with confirmed immunohistochemistry or in situ hybridization.
    c. Measurement of BKV VP1 mRNA in urinary cells
    d. Identification of Decoy cells in urine
    e. Quantitative viral load in plasma with a threshold of >10,000 copies of BKV per ml of plasma
5. Hemorrhagic cystitis and necrotizing hemorrhagic tubulointerstitial nephritis are occurred exclusively asoociated with a viral infection which is...
    a. Cytomegalovirus
    b. BK virus
    c. Adenovirus
    d. Parvovirus B19
    e. Varicella zoster virus

ท่านที่ประสงค์จะได้รับเครดิตการศึกษาต่อเนื่อง (CME credit)
กรุณาส่งคำตอบพร้อมรายละเอียดของท่านตามแบบฟอร์มด้านหน้า

ศาสตราจารย์นายแพทย์สุทธิพร จิตต์มิตรภาพ
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