Viral Nephropathies: Core Curriculum 2024

Amy A. Yau, Sangeetha Murugapandian, Ali W. Rizvi, and Anna Gaddy

Viral-associated nephropathy is when kidney disease results from active viral replication. Because of the high global burden of viral infections, clinicians should be aware of their incidence, kidney manifestations, mechanism of injury, and management. Some viruses, such as hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can lead to nephropathy more commonly than other endemic viruses, such as Epstein-Barr virus, cytomegalovirus, and polyoma virus which are more important causes of nephropathy in the immunosuppressed patient. Other viruses, such as hantavirus and dengue virus, have a high global infectivity rate with rare but severe kidney manifestations. Advances over the past decades have offered us a better understanding of the pathogenesis of viral-associated nephropathies and antiviral therapy options. The patterns of kidney injury include glomerular and tubulointerstitial lesions in the setting of acute and chronic infection. Direct viral infection of kidney parenchymal cells may drive pathologic findings, but kidney pathology may also result from indirect mechanisms due to activation of the innate and adaptive immune system. Some viruses can cause kidney injury due to altered hemodynamics from liver dysfunction or shock. More information about the role of genetics, specifically *APOL1* polymorphisms, has come to light in regard to HIV-associated nephropathy and SARS-CoV-2–associated nephropathy. Advances in antiviral therapy help reduce nephrotoxicity and improve morbidity and mortality. In this Core Curriculum, we review common viruses responsible for kidney disease worldwide, discuss mechanisms of pathogenesis, and highlight specific management principles of viral nephropathies. We also discuss other viruses with high endemicity despite low incidence of kidney disease in the immunocompetent and immunosuppressed host.

Complete author and article information provided at end of article.

Correspondence to A.A. Yau (amy.yau@osumc.edu)

Am J Kidney Dis. 84(6):767-779. Published online October 10, 2024.

doi: 10.1053/j.ajkd.2024.06.014

Introduction

Despite public health efforts to improve the detection and reduce the transmission of viral infections and despite advances in antiviral therapy, the global burden of viral illnesses remains high. There are 1.5 million new cases of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) each year. Nearly 300 million people worldwide are infected with chronic hepatitis B virus (HBV), and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic has been responsible for over 6.9 million deaths to date since 2019. All these viruses are associated with kidney disease and injury. But advances in our understanding of viral pathogenesis and the rise of newer antiviral therapies have changed the landscape of kidney disease associated with these viruses. Some viruses are being eradicated or suppressed more effectively, changing the natural history of associated kidney diseases. Indeed, in the United States kidney transplant organs can now come from HCV-positive and HIV-positive donors, increasing the pool of donors for people with end-stage kidney disease (ESKD).

To attribute kidney disease to viral infection requires fulfillment of certain criteria. This includes clinical manifestations, specific serologic testing, identification of viremia, and detection of the viral antigen/host antibody in the kidney histology. Although ideally the resolution of kidney injury will follow the resolution of infection, this may not always occur, depending on the mechanism and severity of the insult. It is worth noting that in addition to viral replication causing kidney disease, the therapies for viral illnesses can also lead to nephrotoxicity. In this installment of *AJKD*'s Core Curriculum in Nephrology series, we address the specific mechanisms by which each of the most common viral illnesses can lead to kidney disease and the current care practice recommendations (Table 1). We also discuss other viruses with high endemicity despite low incidence of kidney disease in the immunocompetent and immunosuppressed host.

Pathogenesis

Viruses can lead to kidney disease through direct and indirect mechanisms (Table 2). Identifying direct viral cell infiltration as a cause of the kidney injury is difficult because tubular uptake of viral proteins or DNA or RNA fragments is common and not necessarily a consequence of direct viral cell infection.

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Table 1. Summary of Common Viral Nephropathies

Virus	Epidemiology	Frequency of Kidney Manifestations	Common Kidney Pathology Findings
Hepatitis B virus (HBV)	296 million people infected worldwide	3%-5% of people with chronic infection	• Membranous nephropathy • MPGN • Polyarteritis nodosa vasculitis
Hepatitis C virus (HCV)	58 million people infected worldwide	1% of people with chronic infection with have glomerular disease and/or vasculitis	MPGN with or without out cryoglobulinemic inclusions
Human immunodeficiency virus (HIV)	37.7 million people affected worldwide	6%-30% of people living with HIV will have proteinuria due to their HIV infection	• Collapsing FSGS • MPGN • TMA • Acute tubular injury with interstitial inflammation
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	760 million people worldwide	46%-77% with kidney injury (majority are due to acute tubular injury)	• Acute tubular injury • Collapsing FSGS • TMA: elevated creatinine with proteinuria and/or hematuria

Abbreviation: FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

However, some viruses do directly invade glomerular, mesangial, and kidney tubular cells, leading to cell damage and death.

Other causes of kidney injury are via indirect methods. One indirect mechanism is immune complex formation due to in situ or circulating immune complexes, which then trigger the host's inflammatory response. A second indirect mechanism includes parenchymal inflammation and kidney endothelial cell injury due to the innate immune response to viral infection, leading to the release of cytokines and chemokines. This can manifest as thrombotic angiopathy and endothelial necrosis. A final indirect mechanism is tubular injury due to hemodynamic compromise, viral-associated rhabdomyolysis, or kidney dysfunction in the setting of liver failure, such as in the setting of HBV or HCV.

For some viral infections, genetic abnormalities that modulate the immune response such as complement factors and *APOL1* polymorphisms may increase the risk and severity of kidney manifestations.

Hepatitis B Virus

Case 1: *A 44-year-old woman presents to the clinic for an evaluation of hematuria and proteinuria. Six months ago she was evaluated for elevated aminotransferases and found to be HBV positive. Her viral load is 30,000 IU/mL and she has tested positive for hepatitis B e antigen (HBeAg). Her*

Table 2. Mechanisms of Viral Nephropathy

Mechanism Types	Examples
Direct Viral Injury	
Podocyte, tubular epithelial cell, endothelial cell invasion	• HIV-associated collapsing glomerulopathy (HIV-associated nephropathy) • Hantavirus-associated tubular injury • BK nephropathy due to viral inclusions of tubular cells
Indirect Viral Injury	
Immune complex deposition	• Hepatitis B–associated membranous nephropathy (in situ) • Hepatitis C membranoproliferative disease with or without cryoglobulinemia (circulating)
Parenchymal inflammation due to cytokine/chemokine release in response to viremia	• HIV-associated tubulointerstitial inflammation in the setting of HIV-associated nephropathy • Epstein-Barr virus tubulointerstitial disease
Endothelial cell injury due to inflammatory response to viremia	• HIV-associated thrombotic microangiopathy • SARS-CoV-2–associated thrombotic microangiopathy
Tubular injury in the setting of secondary effects of viral infection (ie liver failure, rhabdomyolysis, altered hemodynamics, etc)	• SARS-CoV-2–associated acute tubular injury • Dengue virus–associated acute tubular injury

hepatologist initiated antiviral therapy. The laboratory evaluation is significant for a serum creatinine level of 1.3 mg/dL (increased from 1.1 mg/dL last year), serum albumin of 3.6 g/dL, and urinalysis with trace blood and 3+ protein. Her 24-hour urine protein is 4.6 g. Her kidney biopsy reveals membranous nephropathy, and serum anti-phospholipase A_2 receptor (PLA_2R) levels are negative.

Question 1: In addition to antiviral therapy, what is the most appropriate addition to her regimen?

(a) Renin angiotensin system (RAS) inhibition
(b) Corticosteroids
(c) Rituximab
(d) Tacrolimus

For this answer to this question, see the following text.

Hepatitis B is an enveloped, double-stranded DNA virus that can cause acute and chronic infections. It is endemic to certain regions of Asia and Africa where it is often transmitted from mother to child during birth. The US Centers for Disease Control and Prevention (CDC) estimates that 880,000 people in the US have chronic HBV infection, as indicated by the presence of the hepatitis B surface antigen (HBsAg). The highest incidence of new infections is found in unvaccinated adults aged 30 to 59 years old. Up to one-third of persons with HBV are coinfected with HCV, and up to 10% of persons with HBV are coinfected with HIV. Even in individuals with an absence of kidney injury, it is important to identify those with co-infection to prevent long-term end-organ damage from these co-infections.

Kidney disease associated with HBV is most common in chronic carriers with replicative HBV infection. Replicative HBV infection is defined as the presence of HBeAg without antibody formation and HBV DNA viral load more than 2,000 IU/mL, though the degree of viremia has only a modest correlation with clinical severity. Although viral DNA has been identified in kidney parenchymal cells, the kidney manifestations of HBV are indirect and related to the immune response to viral infection. There is a wide range of kidney pathology: membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, secondary focal segmental glomerulosclerosis (FSGS), polyarteritis nodosa (PAN), or cryoglobulinemic vasculitis. Minimal change disease is a rare manifestation of HBV.

Membranous nephropathy is the predominant form of glomerular pathology linked to HBV. The pathophysiology of HBV-associated membranous nephropathy is the formation of in situ immune complexes against HBeAg. Because of its size and negative charge, HBeAg can cross the glomerular basement membrane and deposit in the subepithelial space where it binds primarily to filtered immunoglobulin G1. The antibody binding triggers complement activation in the urinary space. Of interest, unlike in primary membranous nephropathy, C3 and C4 levels may be reduced in HBV-associated nephropathy. Immune complex deposits of HBsAg and HBcAg can also be found in conjunction with HBeAg.

Interestingly, some cases of HBV-associated membranous nephropathy exhibit strong PLA_2R staining alongside HBsAg or HBcAg. PLA_2R is the most common target of primary membranous nephropathy. Of patients with positive PLA_2R Ag staining, the majority have circulating anti-PLA2R antibodies, and it is unclear whether this represents primary membranous nephropathy in the setting of HBV viremia or this reflects secondary membranous nephropathy as a consequence of exposed podocyte epitopes triggering anti-PLA_2R. Either way, patients with HBV-associated nephropathy and PLA_2R positivity have a more favorable prognosis after antiviral therapy.

HBV-associated MPGN and IgA nephropathy present with varying degrees of hematuria, proteinuria, and reduced kidney function. Despite antiviral and immunosuppressive therapy, more than 50% of patients with HBV-associated MPGN progress to ESKD. Affected patients are HBsAg positive but HBeAg negative, with variable antibodies to hepatitis B core antigen (anti-HBc). Deposition of circulating immune complexes and formation of in situ immune complex in the subendothelial space contribute to the pathogenesis of HBV-associated MPGN. The mechanism of HBV-related IgA nephropathy is unclear. Theories include IgA deposition due to impaired hepatic metabolism of IgA, IgA antibody response to HBV Ag in the mesangium, or a primary IgA nephropathy in the setting of HBV viremia, especially in endemic areas.

PAN, a necrotizing vasculitis of small and medium blood vessels, and mixed cryoglobulinemia are both described, but mixed cryoglobulinemic vasculitis is more common in the setting of HCV compared with HBV. HBV-associated PAN develops within 4 months after HBV infection and is associated with high viral loads. Although kidney involvement is common, kidney insufficiency is rare but more common if an HBV infection remains untreated. The incidence of HBV-associated PAN is decreasing as vaccination rates in endemic areas start to rise. Symptoms of kidney involvement include hematuria, mild proteinuria, and hypertension. Glomerular involvement is rare, but some patients may present with kidney infarcts, life-threatening ruptured aneurysms, or spontaneous perirenal hemorrhages. Vasculitis in HBV-associated PAN is triggered by immune complexes in blood vessel walls leading to complement activation and necrosis. It is not clear which antigen leads to the development of HBV-associated PAN.

Management of HBV-associated kidney disease is focused on antiviral therapy against HBV. Antiviral therapy is also important to prevent hepatitis flares and reduce the risk of liver failure. However, in children with HBV-associated membranous nephropathy, treatment is conservative because spontaneous remission due to antibody formation to HBeAg (anti-HBe) is common. This is in contrast to adults where spontaneous resolution and

seroconversion are rare. Nearly one-third of adult cases progress to ESKD without antiviral therapy.

There are multiple therapy options for replicative HBV, including nucleotide and nucleoside reverse transcriptase inhibitors and interferon. Nucleoside analogues such as lamivudine, telbivudine, and entecavir result in sustained viral remission (SVR) in 85% of patients; pegylated interferon induces SVR in only 60% of patients. When interferon or lamivudine antiviral therapy was compared with steroid use alone, antiviral therapy had higher rates of HBeAg clearance and remission of proteinuria; lamivudine, the most commonly used agent, can lead to complete resolution of associated membranous nephropathy. There is also some suggestion that lamivudine and steroid combination therapy is beneficial in HBV-associated IgA nephropathy.

Despite the treatment options, cure of HBV viremia is challenging because of resistance to therapy and integration of the viral genome into the host genome, resulting in viral dormancy. Other challenges with therapeutics include dose adjustment for many in the setting of kidney dysfunction because many of these agents are filtered and secreted by the organic anion transporters in the proximal tubule, and nephrotoxicity may result from long-standing use of certain antivirals such as adefovir and tenofovir disoproxil fumarate (TDF). Interferon is not well-tolerated and may lead to further stimulation of the immune response and worsen end-organ manifestations of replicative HBV. These data, which are further described in the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines, further support the use of antiviral therapy for HBV-associated kidney disease.

Additional immunosuppressive therapy outside of antiviral therapy is not routinely recommended. Cyclophosphamide and rituximab can accelerate HBV replication in untreated replicative HBV or can reactivate dormant or occult HBV. In patients with PLA_2R-positive membranous nephropathy and replicative HBV, the recommendation is to treat the virus first before considering immunosuppressive therapy. If patients present with MGPN or PAN with severe manifestations, immunosuppressive therapy with or without plasmapheresis can be considered in conjunction with antiviral therapy. Plasmapheresis can also be considered in systemic cryoglobulinemic vasculitis, especially if plasma cryoglobulin levels are high. Calcineurin inhibitors may be utilized in HBV-associated membranous nephropathy or FSGS to help reduce proteinuria. Unlike other immunosuppressive agents, there is some suggestion that calcineurin inhibitors reduce viral replication through inhibition of HBV cell entry. All in all, the data on the routine use of immunosuppressive therapy in addition to antiviral therapy for HBV-related glomerular disease are limited.

For our patient, in addition to treatment of her chronic HBV, the next best step in management is to start an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), given the presence of significant proteinuria. Thus, the correct choice is (a) RAS inhibition. Routine immunosuppressive therapy is not recommended.

Additional Readings

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Hepatitis C Virus

Case 2: *A 61-year-old man with a 20-year history of well-controlled diabetes mellitus and no known history of microalbuminuria is presenting for a follow-up evaluation of his proteinuria. His physical examination is unremarkable. His laboratory results are notable for a hemoglobin A_{1C} that has always been less than 6.5%. His annual laboratory results show a serum creatinine of 1.2 mg/dL and a urinalysis significant for blood with 3 red blood cells per high power field and 2+ proteinuria. His random urinary protein-creatinine ratio was measured at 1.0 mg/mg. Last year he had no proteinuria. Further testing is positive for hepatitis C antibody and positive hepatitis C viral load.*

Question 2: What is the next best step in this patient's care?

(a) Referral for hepatitis C treatment
(b) Initiation of steroids and plan for kidney biopsy
(c) Initiation of rituximab and plan for kidney biopsy
(d) Initiation of finerenone for diabetic kidney disease

For this answer to this question, see the following text.

Globally, an estimated 58 million people are infected with HCV, a small single-stranded RNA virus, with about

1.5 million new infections occurring each year. An estimated 3.2 million adolescents and children live with chronic hepatitis C infection, and its prevalence among patients receiving maintenance dialysis is between 5% and 25%, depending on geographical location. The vast majority of kidney injury in patients with HCV is related to liver disease, but chronic viral infection leading to sustained immune-related glomerular disease can occur in a minority of patients.

The most common etiology of viral-induced kidney injury is immune complex–mediated damage to the glomerular basement membrane with subsequent membranoproliferative glomerulonephritis (MPGN), seen decades after the initial infection. Classically this MPGN pattern is associated with cryoglobulinemia. Immune complexes can also deposit in blood vessels and cause PAN with kidney ischemia. Less common manifestations include IgA nephropathy, membranous nephropathy, FSGS, and immunotactoid and fibrillary glomerulonephritis.

Kidney injury associated with cryoglobulinemic vasculitis may manifest as a nephritic or nephrotic syndrome, and kidney pathology findings reveal an MPGN pattern of injury. In addition to HCV's predilection for invasion of hepatocytes, HCV is also lymphotropic and can bind directly to B cells. In contrast, HBV cannot enter lymphatic tissue and thus less often leads to cryoglobulinemia. B-cell stimulation by HCV produces a type III (polyclonal) IgMκ and a polyclonal IgG; this mixture of IgM and IgG components, type II and type II cryoglobulins, are termed mixed cryoglobulinemia. The development of cryoglobulinemia occurs in up to half of HCV-infected patients after 5-10 years of infection. Over additional years, a small proportion of these patients will begin to form type II cryoglobulins, which are composed of a mixture of monoclonal IgM with rheumatoid factor (RF) activity and polyclonal IgG. When this happens, the entire monoclonal IgMκ fragment plus the IgG component plus certain HCV proteins form a complex that deposits in the subendothelial space.

Chronic infection leads to waves of immune complex deposition and complement activation, which results in thickening and splitting of the glomerular basement membrane with IgG, IgM, and C3 deposition and even intraluminal occlusion. Glomeruli may be hypercellular and have lobular tufting. In cases of cryoglobulin precipitation, electron microscopy can reveal curved microtubules in the subendothelial deposits with a characteristic fingerprint pattern. Because tissue destruction happens over years of infection as the result of prolonged complex deposition and complement activation, other signs of chronicity such as glomerular and mesangial sclerosis are to be expected. Patients with mixed cryoglobulinemia can have extrarenal manifestations with associated purpura, skin ulcers, peripheral neuropathy, and arthralgias. In 30% of patients with mixed cryoglobulinemic vasculitis, mixed cryoglobulin complexes deposit in the kidney.

Another cause of vasculitis in HCV is PAN. HCV-associated PAN occurs at much lower frequency than HBV-associated PAN. Typically, it occurs 2 to 3 years after infection with HCV, and nearly a quarter of studied patients with HCV-associated PAN were also positive for HBsAg. The exact mechanism of HCV-associated PAN is unclear, but not related to cryoglobulinemia. The incidence of IgA nephropathy in patients with HCV is limited to case reports, and the presentation is similar to noninfected hosts. Membranous nephropathy is more common in transplant recipients infected with HCV, though highly effective treatment regimens have likely diminished the importance of this finding.

Direct-acting antiviral (DAA) therapy has revolutionized the care of patients with HCV. It has a SVR rate more than 95% and a mild side-effect profile, especially compared with prior interferon-based regimens. DAA therapy targets nonstructural proteins important for HCV replication. Because the treatment for HCV-related glomerulonephritis is treatment of the virus and because therapy is so well-tolerated, a patient with untreated HCV and features of glomerular disease can be treated without biopsy. If a patient experiences more rapid kidney disease progression while on DAA or if the diagnosis is unclear, biopsy should be considered.

If a patient experiences an acute severe vasculitis, immunosuppression may be needed in addition to DAA because DAA does take 1-2 months to cause clearance. For these patients, cyclophosphamide-based regimens have been used for patients with RPGN with or without vasculitis; however, rituximab-based regimens are now heavily favored given their impressive clinical trial results in patients with mixed cryoglobulinemia. It is worth noting that not all patients in these trials had kidney involvement, but review of the individual cases with kidney involvement showed 85% of patients had either a partial or complete clinical response. In parts of the world where DAA therapy is not available or when interferon-based therapy is used for other reasons, it is important to remember interferon alpha and ribavirin must be dose adjusted for decreased kidney function. If given after kidney transplant, these older regimens can trigger kidney transplant rejection.

In patients with advanced kidney disease, a multidisciplinary discussion about transplant options and treatment of HCV before transplantation should guide shared decision making. Because the success rate of DAA therapy is so high, delaying treatment until after transplant can increase the pool of potential organs to include HCV-positive donors. However, DAA can cause interactions with calcineurin inhibitors and given the unpredictable nature of wait times for deceased-donor organs, treating patients before donation is a reasonable strategy as well. The decision surrounding treatment timing is based on the availability of infected versus noninfected donors, local policy, risk of allograft dysfunction, and patient preference.

Because the patient in this case has relatively mild kidney disease and had not been treated for hepatitis C, he requires choice (a), treatment of hepatitis C. Although a kidney biopsy could be used to differentiate between diabetic kidney disease, other glomerulonephritis, and HCV-related glomerulonephritis in this patient, it would not be appropriate to delay treatment of his HCV. Additionally, his diabetes mellitus is of long-standing and is well-controlled, making it less likely to be the source of his kidney disease. Empiric treatment for HCV-related glomerulonephritis (choices b or c) would not be appropriate given the possibility of improvement with DAA alone; in these cases, biopsy would be recommended. Treatment specific for diabetic kidney disease (choice d) is appropriate only after HCV-related disease has been excluded or treated.

Additional Readings

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Human Immunodeficiency Virus

Case 3: *A 45-year-old woman is hospitalized for pneumonia and an elevated creatinine level. Two years ago, her creatinine was 1.4 mg/dL with urine dipstick positive for protein. On evaluation today, she has significant lower extremity edema, her creatinine is 2.8 mg/dL, and her 24-hour urine reveals 4.1 g of protein. There is no family history of kidney disease. On evaluation, the HIV screen is positive, with a viral load of 158,000 copies/mL with a CD4 count of 164 cells/mm^3. The complete blood count is otherwise normal. She undergoes a kidney biopsy, and the pathology findings show collapsing FSGS.*

Question 3: What is the next best step in management?

(a) Begin combined antiretroviral therapy (cART)
(b) Start prednisone at 1 mg/kg
(c) Prescribe a calcineurin inhibitor
(d) Refer for kidney transplant

For this answer to this question, see the following text.

HIV is a single-strand enveloped RNA retrovirus that upon entry to the target cell utilizes the cells' machinery to increase viral proteins and help with replication. After infection, the virus maintains a sustained immune response leading to immunodeficiency and T-cell depletion. HIV-1 has high virulence and infectivity and is the leading subtype worldwide. In 2020, there were 37.7 million people worldwide living with HIV, and 1.5 million newly infected people. People living with HIV can develop different kidney manifestations depending on the chronicity of disease and immune status, although the spectrum of kidney biopsy findings have changed in the era of cART. Still, people living with HIV have an 11-fold increase incidence of chronic kidney disease (CKD). In the modern cART era, the annual incidence of ESKD in people living with HIV has plateaued.

Early in the epidemic, before the current diagnostic and therapeutic options, the most common kidney pathology lesion was collapsing FSGS, termed HIV-associated nephropathy (HIVAN). HIVAN occurs in the context of uncontrolled HIV viremia and low CD4 counts less than 200 cells/mm^3, and these patients present with nephrotic-range proteinuria with or without edema and rapidly declining kidney function. Most cases of HIVAN have been described in individuals of West African ancestry; in the United States, more than 90% of HIVAN-associated ESKD cases are African American. The risk of HIVAN in patients of West African ancestry is increased 12.2-fold compared with other racial groups, likely related to the high prevalence of *APOL1* polymorphisms. *APOL1* homozygous individuals living with HIV have a 50% lifetime risk of developing HIVAN in the absence of therapy compared with individuals with 0 or 1 risk allele. Before the widespread use of cART, the prevalence of HIVAN on biopsy was anywhere from 40%-80%, but now HIVAN is reported in around 14%-35% of biopsies; the most recent 2020 Columbia University registry noted HIVAN in only 14% of biopsies performed in people living with HIV. Many other viruses, such as SARS-CoV-2, EBV, and parvovirus B19 are also associated with collapsing FSGS, and it is likely *APOL1* polymorphisms play a role in these entities as well.

HIVAN is caused by direct viral infection of podocytes, mesangial cells, and tubular epithelial cells. It is not clear how the virus enters cells, but it does not rely on the typical CD4 and CCR5/CXCR4 interface. Viral entry may be through other CD4-independent pathways or infected macrophages and lymphocytes or through endocytosis of apoptotic HIV lymphocytes. The HIV virus then utilizes cell machinery to express viral proteins which lead to abnormal cell maturation and de-differentiation of cells, leading to

"dysregulated podocytes," foot process effacement, and collapse of glomerular capillaries. Interferon-mediated *APOL1* expression in podocytes and parietal epithelial cells may result in abnormal endolysosomal function, altered autophagy, and cell death. These factors may allow HIV to persist within podocytes and cause further cell dysregulation or lead to more inflammatory-mediated cell death.

The second most common lesion in people living with HIV is HIV immune complex disease (HIV-ICD). HIV-ICD is an umbrella diagnosis, and a 2020 Columbia University registry noted HIV-ICD in 17% of kidney biopsies. The pattern seen on biopsy can be a MPGN akin to lupus-like glomerulonephritis with "full house" immunofluorescence, post-infectious glomerulonephritis, or IgA nephropathy or membranous nephropathy pattern. Immune complex deposits can be subendothelial, intramembranous, or subepithelial. Clinical manifestations include proteinuria, hematuria, reduced kidney function, and low complement levels. It is unclear if the immune complex deposition is from circulating or in situ immune complex formation. In patients with active HIV viremia, immunoglobulins may respond to HIV antigens, perhaps p24 or gp120, and RNA load is usually more than 400 copies/mL. In a patient with well-controlled HIV, immune complex deposition may be related to other bacterial or viral antigens. HIV-ICD impacts all demographics equally and has a lower incidence of ESKD compared with HIVAN. People living with HIV and with kidney injury should also be tested for co-infection of HBV and HCV.

Other kidney histopathologic findings are tubulointerstitial disease, vascular, or glomerular disease from co-infection of HBV and HCV. Tubulointerstitial disease can result from the release of chemokines and cytokines from the innate immune cells (monocytes, macrophages, and CD8-positive T cells) in response to HIV, resulting in interstitial inflammation and fibrosis. This persistent cytokine response, namely via interferon gamma, can result in the development of tubuloreticular inclusions seen on electron microscopy. Although HIV can also reside dormant in kidney tubular cells and be transmitted from kidney cells to circulating T cells and monocytes, there is no evidence for direct tubular cell to tubular cell transmission.

Microcystic dilation on biopsy can be seen due to proliferation of tubular epithelial cells which causes kidneys to appear enlarged and echogenic on ultrasound imaging. Thrombotic microangiopathy (TMA) may be seen in advanced untreated HIV with low CD4 counts due to endothelial damage from HIV protein-mediated inflammatory response. Additional factors such as antiphospholipid antibody syndrome may contribute. Some patients with TMA have systemic manifestations such as thrombotic thrombocytopenic purpura (TTP) with low ADAMTS13 (von Willebrand factor protease) levels, but these individuals had less advanced disease and a better prognosis than those with normal ADAMTS13 levels. As described earlier, tubulointerstitial inflammation is often seen in the context of HIVAN, or can be related to cART, or may occur in response to secondary bacterial or viral infections.

The mainstay of treatment for people living with HIV and kidney-related manifestations includes cART, regardless of CD4 count. Combined ART includes a 2- or 3-drug regimen consisting of nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and integrase strand transfer inhibitors (ISTI). An alternative regimen based on protease inhibitors (PI) can be used in treatment-naive patients as well. Control of viremia reduces glomerular and tubular lesions in HIVAN. However, it is unclear whether cART can prevent or ameliorate HIV-ICD because the incidence of HIV-ICD has been stable despite the advent of cART. In the pre-cART population, patients on RAS inhibition had longer mean kidney survival before ESKD. Steroids were sometimes utilized in the treatment of HIVAN to quell tubulointerstitial inflammation. In the cART era, there is limited benefit of corticosteroids, and their routine use may increase the risk of opportunistic infections. RAS inhibition is appropriate for those with hypertension and/or proteinuria.

Antiviral therapies are also associated with nephrotoxicity (Table 3), and a thorough and detailed history is

Table 3. Kidney Complications of Antiviral Therapy

Drug Class	Drug	Nephrotoxicity
Fusion inhibitors	Maraviroc	Postural hypotension (adverse effects usually resolve after discontinuation)
NRTI	Abacavir	Abacavir hypersensitivity syndrome with acute interstitial nephritis
	Tenofovir disoproxil fumarate	Tubular toxicity, proximal tubulopathy syndrome
NNRTI	Efavirenz	Rare cases of acute interstitial nephritis and hypersensitivity
ISTI	Dolutegravir, bictegravir	Inhibit tubular secretion of serum creatinine
PI	Atazanavir, indinavir	Nephrolithiasis, crystalluria, indinavir papillary necrosis
Other	Acyclovir	Crystalluria with IV use
	Cidofovir	Proximal tubulopathy, acute tubular necrosis
	Cobicistat	Inhibits tubular secretion of serum creatinine
	Foscarnet	Acute tubular necrosis, nephrogenic diabetes insipidus
	Ritonavir	Inhibits tubular secretion of serum creatinine

Abbreviations: ISTI, integrase strand transfer inhibitors; IV, intravenous; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

important to determine the etiology of kidney disease in the era of cART. Both TDF and tenofovir alafenamide (TAF) are also used as part of cART. In particular, TDF can cause a proximal tubulopathy. TAF is less nephrotoxic, likely because it is used in lower doses and is more stable in serum so a higher percentage of the ingested dose is delivered to lymphocytes. Integrase inhibitors may cause elevations in serum creatinine due to impaired creatinine secretion, but they are not nephrotoxic.

Given our patient's kidney biopsy findings and new diagnosis of HIV, it is likely her collapsing FSGS is due to the previously undiagnosed HIV infection. In addition to conservative therapies such as RAS inhibitors, answer (a) is appropriate: cART should be started as soon as possible. Immunosuppression and referral for kidney transplantation would be premature at this juncture.

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SARS-CoV-2

Case 4: *A 22-year-old man with obesity presents with somnolence, hypotension, and hypoxia. He is intubated for hypoxemic respiratory failure; after fluid resuscitation, he is started on norepinephrine for persistent hypotension. Laboratory testing is positive for SARS-CoV-2 and for a serum creatinine of 2.5 mg/dL. He is anemic with a haptoglobin of 45 mg/dL and ferritin of 1,000 ng/mL. His urinalysis is significant for hematuria and 2+ proteinuria. Kidney biopsy identifies TMA.*

Question 4: What is the best therapy to improve kidney outcomes in this patient?

(a) Corticosteroids
(b) Supportive care
(c) Eculizumab
(d) Plasmapheresis

For this answer to this question, see the following text.

The SARS-CoV-2 is an enveloped single-stranded RNA coronavirus that led to a global pandemic in 2019 resulting in a state of emergency for 3 years. Much of our understanding of kidney disease associated with SARS-CoV-2 infection is related to the first and most serious wave of SARS-CoV-2. According to the World Health Organization, as of 2023 the virus had caused over 6.9 million deaths worldwide and infected over 760 million people. Much of the morbidity and mortality early in the pandemic was associated with non-omicron variants and unvaccinated patients.

In people with SARS-CoV-2 infection, roughly one-third of hospitalized patients experienced kidney injury, and the rates were higher for patients in the intensive care unit. Patients with kidney injury had an increased mortality rate. The risk factors for developing kidney injury included patients with CKD, obesity, underlying diabetes mellitus or cardiac disease, and older age. As the pandemic progressed, the mortality and rates of kidney injury for people with SARS-CoV-2 decreased. This is likely due to a variety of factors, including improved understanding of transmission and implementation of public health and safety measures, rise of new viral variants of decreased virulence, changes in therapy to include restrictive fluid strategies, improved therapeutics, and widespread vaccination against SARS-CoV-2.

Kidney biopsies performed on autopsy largely found that the pathology is consistent with acute tubular injury. However, it is unclear whether the presence of viral cell entry is an important contributor to injury or whether injury is entirely related to indirect factors such as the inflammatory response, altered hemodynamics, or endothelial dysfunction from viremia. Although viral particles in kidney tubular epithelial have been reported, there are opposing reports on the presence or absence of viral RNA in kidney cells. However, there is some evidence that suggests tropism for SARS-CoV-2 to kidney proximal tubular cells, and direct infectivity leading to apoptosis and necrosis.

It is postulated that the virus enters kidney cells via endocytic and nonendocytic pathways. ACE2 is a membrane-bound protein commonly found in kidney proximal tubular cells, and some are present on the

podocyte. Endocytosis can occur after binding to ACE2, but direct viral RNA entry from viral capsid into kidney cell cytoplasm requires a cofactor TMPRSS2. There was some speculation on whether ACE inhibitors may impact kidney outcomes in patients, but 2 large observational studies, REPLACE COVID and BRACE CORONA, showed no clear association between the use of ACE inhibitors and the susceptibility or severity of SARS-CoV-2 infection or kidney outcomes.

The second mechanism of kidney injury is indirect tubulointerstitial inflammation and fibrosis and TMA as a result of release of cytokines from the innate immune response to viremia. Tubular injury can also be a direct result of toxicity from myoglobulin in the setting of rhabdomyolysis, but the mechanisms of SARS-CoV-2–mediated rhabdomyolysis is unclear.

Early in the pandemic, patients were found to be hypercoagulable, and in addition to tubular injury evidence of TMA was identified on kidney biopsy. TMA can occur at the time of SARS-CoV-2 infection and up to 1 month after viral clearance, and it may be associated with thrombotic thrombocytopenic purpura (TTP) or atypical hemolytic uremic syndrome (aHUS) or kidney limited. Most patients with SARS-CoV-2–associated TMA had gastrointestinal rather than pulmonary symptoms. Up to 50% of individuals with SARS-CoV-2–related aHUS had evidence of dysregulation of the alternative complement pathway or an already known genetic complement abnormality suggesting SARS-CoV-2 was a "second hit" event. The pathogenesis of endothelial dysfunction is unclear but thought to be due to an enhanced inflammatory response leading to endothelial injury and subsequent inflammatory response, or due to the viral spike protein–mediated changes in whole blood and fibrin formation with impaired fibrinolysis. However, abnormalities in complement activation may also lead to an excess of C5a, which can bind tubular epithelial and endothelial cells resulting in cell atrophy and kidney fibrosis.

Outside of tubular and vascular injuries, glomerular lesions were also found in patients with SARS-CoV-2–associated kidney injury. Of patients undergoing diagnostic kidney biopsy, a majority of the patients had collapsing FSGS (Fig 1), and 9% had TMA. Again, it is unclear whether this is due to direct viral infection of the podocytes or indirect response from the inflammatory response triggered by viremia. Like HIVAN, SARS-CoV-2–related collapsing glomerulopathy, sometimes termed COVAN, is found almost exclusively in people of African descent with *APOL1* risk alleles, and it often presents as nephrotic range proteinuria. Other glomerular lesions such as minimal change disease, membranous nephropathy, and lupus-like nephritis have been reported and likely occur through activation of the immune system.

Treating acute kidney injury in the setting of SARS-CoV-2 is largely supportive. There were some suggestions that C5 inhibitor therapy may be helpful in severe SARS-CoV-2 with TMA, but the study population was small. Prophylactic anticoagulation was helpful in an US Veterans Affairs database in patients with moderate SARS-CoV-2 pneumonitis, but not in critically ill patients. It is also unclear whether antiviral therapy for SARS-CoV-2 with Paxlovid (nirmatrelvir and ritonavir), tocilizumab, or remdesivir help to reduce the incidence or prevalence of acute kidney injury or CKD in infected patients. However, remdesivir has been found to help treat SARS-CoV-2–related acute kidney injury in patients without concomitant liver disease. Nephrotoxicity of antiviral therapy has been reported, but exact mechanisms remain unclear. In Case 4, the patient has kidney-limited TMA; because there are no proven therapies to impact kidney outcomes, the answer is (b), supportive care.

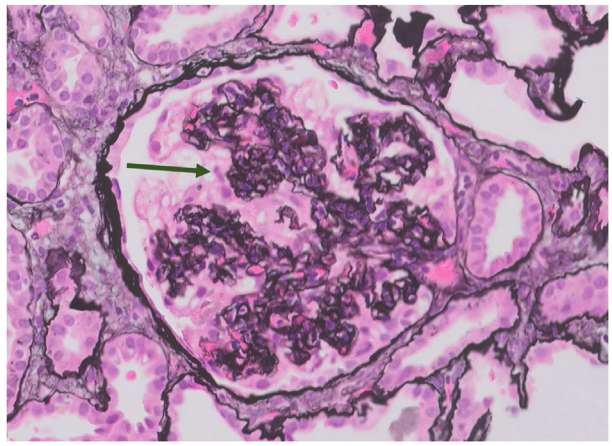

Figure 1. Example of collapsing secondary focal segmental glomerulosclerosis lesion in a patient with SARS-CoV-2 infection. Light microscopy silver stain showing areas of glomerular collapse (arrow). Original magnification, ×400. Image © 2024 Anjali A. Satoskar, MD and is reproduced with permission of the copyright holder.

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Other Viral Nephropathies

Case 5: *A 35-year-old woman with a history of hematopoietic stem cell transplant 10 years ago for acute lymphocytic leukemia now presents for evaluation of kidney injury. Her serum creatinine level over the past 5 years has slowly increased from 0.8 mg/dL to 1.8 mg/dL. Her urinalysis is negative for proteinuria or hematuria. She remains on tacrolimus for graft versus host disease, with tacrolimus troughs 4-5 ng/mL. She feels well other than some fatigue and had an incidental finding of nonspecific intra-abdominal lymphadenopathy on a computed tomography scan performed for vague abdominal pain last month.*

Question 5: What additional test would be helpful to diagnose the cause of her symptoms?

(a) Parvovirus B19 immunoglobulin G
(b) Serum EBV polymerase chain reaction (PCR)
(c) Urine adenovirus PCR
(d) Serum BK virus PCR

For this answer to this question, see the following text.

Numerous other viruses are associated with kidney injury. We will highlight some viruses that have a high global incidence but perhaps lower incidence of kidney impairment and others that are endemic and manifest kidney injury mainly in the immunosuppressed patient (Table 4), excluding those with solid organ transplant.

Hantavirus is an enveloped single-stranded RNA virus can lead to 2 main clinical syndromes: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). The highest reported incidence is in the People's Republic of China, where up to 100,000 or more cases of HFRS are reported annually. According to the CDC, from 1993 to 2021 there have been 821 cases of HPS in

Table 4. Summary of Other Viral Infections and Associated Nephropathies

Virus	Epidemiology	Frequency of Kidney Manifestations	Common Kidney Pathology Findings
Hantavirus	More than 200,000 people worldwide each year	Majority of patients with symptomatic infection	• Acute tubular injury with interstitial nephritis • Mesangial proliferative glomerulonephritis
Dengue virus	Estimated 390 million people worldwide (around 100,000 people with symptoms)	15% of patients with symptomatic infection	• Acute tubular injury • Mesangial proliferative glomerulonephritis
CMV	More than 80% seroprevalence by adulthood worldwide	Rare kidney involvement	• Tubulointerstitial nephritis • Intranuclear and cytoplasmic inclusion bodies in kidney tubular epithelial and endothelial cells • Rare reports of collapsing FSGS and other glomerulopathies
EBV	More than 80% seroprevalence by adulthood worldwide	Rare kidney involvement	• Tubulointerstitial nephritis, may have atypical lymphoid cells or plasma cells • Membranoproliferative glomerulonephritis • Some reports of collapsing FSGS, minimal change disease, and other glomerulopathies
Parvovirus B19	70%-85% seroprevalence by adulthood worldwide	Rare kidney involvement in the nonimmunosuppressed population	Collapsing FSGS
BK (polyoma) virus	80%-90% seroprevalence by adulthood worldwide	Rare kidney involvement described in immunosuppressed patients (excluding kidney transplant recipients)	• Viral inclusions in kidney tubular epithelial cells with interstitial inflammation, positive for SV40 on immunohistochemistry • Acute tubular injury

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; FSGS, focal segmental glomerulosclerosis.

the United States. Both syndromes manifest with fever, capillary leak, and cardiopulmonary insufficiency.

In HFRS, endothelial injury due to direct viral infection of cells activates classic and alternative complement pathways and results in capillary leak. Due to direct viral infection of kidney cells, indirect tubular damage in the setting of altered hemodynamics and indirect tubulointerstitial damage due to leukocyte recruitment and cytokine release, acute tubular necrosis, and tubulointerstitial inflammation are the predominant diagnoses on kidney histopathology.

Clinically, patients will have reduced kidney function and oliguria. Urinary manifestations depend on kidney pathology findings, which can persist for months or years after infection. When glomerular involvement predominates, immune complex mesangial proliferative glomerulonephritis with C3 and IgM deposits occurs in response to an activated complement system that is triggered by the innate immunity responding to viremia. Although direct viral infection of endothelial and mesangial cells is described in hantavirus infection, the degree to which direct viral infection contributes to the pathogenesis of glomerular lesions is unclear. Treatment against hantavirus and associated nephropathy is supportive.

Dengue virus is another enveloped single-stranded RNA virus, and infection presents with fever, myalgias, and headache. Some individuals may develop severe dengue after the fever has remitted with main symptoms of abdominal pain and hematemesis. The CDC estimates 390 million annual infections globally, and in 2023 there were a total of 2,884 cases of Dengue virus infection in the United States alone. Only a fourth of patients with dengue infection will develop symptoms, and an estimated 0.01% of individuals will die from severe dengue.

Acute kidney injury is described in approximately 15% of dengue virus cases. Clinical manifestations include hematuria and subnephrotic range proteinuria, although the main finding on biopsy is acute tubular necrosis related to hypovolemia, capillary leak, and/or rhabdomyolysis. There are reports of diffuse mesangial proliferative glomerulonephritis with immune complex and IgM deposition, but the mechanism is not clear. Some studies have demonstrated dengue viral antigens in kidney tubular epithelial cells, but it is unclear whether this is due to direct viral invasion or expression of viral fragments after phagocytosis of degraded virus. Treatment is supportive.

EBV and cytomegalovirus (CMV) are endemic herpesviruses with a global seroprevalence of over 80% in the general population. In immunocompetent individuals, symptoms are mild. After initial infection, EBV remains dormant in memory B cells. CMV has a tropism for endothelial and epithelial cells and can remain latent in various organ tissue. However, there are case reports and case series of kidney complications such as proteinuria and hematuria in the immunocompetent host, specifically in children.

On pathology, interstitial nephritis is described in patients with chronic EBV infection, predominantly with suppressor/cytotoxic T cells but rarely the infiltrate can be mononuclear. Rare glomerular lesions such as immune complex–mediated glomerulonephritis, minimal change disease, and IgA nephropathy have been described. The mechanism of kidney involvement is not clear. Interstitial findings are thought to be due to lymphocyte activation of expressed antigen on tubular cells, but it is unclear whether antigens are related to direct viral infection, although EBV DNA has been detected in kidney tissue in idiopathic acute and chronic interstitial nephritis. Glomerular lesions may be related to anti-EBV cross reacting with podocyte proteins.

Treatment is supportive, but there are case reports that steroid and antiviral therapy with acyclovir may resolve kidney injury, especially in those who also present with severe extrarenal manifestations. Immunocompetent hosts with CMV infection also rarely have kidney involvement. Many reported cases are in the setting of congenital CMV infection. Congenital CMV infection is asymptomatic in over 90% of infants despite persistent viruria for many years. Those with symptoms typically present with growth restriction, hepatosplenomegaly, jaundice, hepatitis, sensorineural hearing loss, and microcephaly. In this setting, immune complex glomerulonephritis is the most common kidney manifestation.

Because of the high seroprevalence in the general population, donors and recipients are screened for EBV and CMV before transplantation to gauge their risk of post-transplant disease. Immunosuppression may allow previously dormant or latent virus to replicate and cause end-organ dysfunction. In the immunosuppressed patient, EBV is classically associated with posttransplantation lymphoproliferative disorder (PTLD). Kidney involvement includes interstitial nephritis with a monoclonal cell infiltrate. Immunosuppressed patients with CMV infection and kidney involvement have been reported to have tubulointerstitial nephritis and collapsing FSGS. It is suspected that local interferon response is responsible for these lesions rather than direct viral invasion despite the presence of intranuclear intracytoplasmic inclusion bodies ("owl eye" inclusions) in the kidney tubular epithelium and identification of viral genome in various kidney cells. The mainstay of therapy in immunosuppressed individuals includes possible reduction of immunosuppression with consideration for rituximab, as in the setting of PTLD, or valganciclovir or ganciclovir based on extrarenal CMV manifestations.

Parvovirus B19 is an endemic DNA virus with a global seroprevalence of 70%-85%, and the virus has a preference for erythroid progenitor cells. Infection frequently causes "fifth's disease" in children and aplastic anemia. Kidney manifestations are rare, even in the immunosuppressed patient. Relatively small studies have suggested an association of parvovirus B19 with collapsing FSGS. The mechanism of kidney injury is unclear, and despite the presence

of parvovirus B19 DNA and proteins present in kidney tissue, it is unclear if direct viral invasion results in podocytopathy. In patients with a nonkidney solid organ transplant, latent parvovirus can become symptomatic within the first year after transplant and manifest as pure red cell aplasia. There is no specific antiviral therapy against parvovirus, but intravenous immunoglobulin can be considered if anemia occurs in immunosuppressed patients.

Unlike EBV, CMV, and parvovirus B19, all viruses with a high endemic seroprevalence that rarely lead to nephropathy in the immunocompetent or immunosuppressed hosts, polyoma virus (BK virus) only leads to nephropathy in the immunosuppressed host. Polyoma virus is a small, icosahedral, double-stranded DNA virus with 80%-90% seroprevalence in adults and remains latent in the genitourinary epithelium. Up to 10% of immunocompetent adults can have asymptomatic viruria.

In nonkidney solid-organ transplant recipients, there is a low incidence of BK nephropathy, suggesting irritation to the genitourinary epithelium may be important to the development of viremia and subsequent nephropathy. But aggressive immunosuppression can allow BK virus replication. In bone marrow transplant recipients 50% of patients will have detectable viruria, and 30% will have detectable viremia within 2 to 8 weeks after transplant. Although rare, in instances of significant immunosuppression, nonkidney solid-organ transplant and bone marrow transplant recipients can develop BK nephropathy of the native kidneys without any prior genitourinary epithelial irritation.

Patients present with reduced kidney function with or without hematuria or proteinuria, and sometimes can have hemorrhagic cystitis. Native BK nephropathy should be suspected in a patient with reduced kidney function in the setting of serum viral load over 1 million copies/mL. The gold standard for diagnosis of BK nephropathy is kidney biopsy, and histology is characteristic for tubular epithelial cell with "ground glass" nuclear inclusion that stain positive against SV40 antigen (Fig 2). SV40 is an immunohistochemical stain developed against polyomavirus simian virus 40, but due to similar characteristics all polyoma viruses will stain positive.

Management of native BK nephropathy, viruria, and hemorrhagic cystitis involves reduction of immunosuppression if possible. Adjunct therapies such as intravenous immunoglobulin, quinolones, cidofovir, and leflunomide have limited efficacy in treatment. Prognosis overall remains poor, depending on the ability to reduce immunosuppression.

Our patient has risk factors for nephrotoxicity, including prolonged calcineurin inhibitor use, but the finding of new lymphadenopathy is concerning for EBV-associated PTLD, with possible associated interstitial nephritis given the limited urinary findings, which makes (b) the correct choice. Other viral infections typically feature proteinuria and/or hematuria, and native BK nephropathy is exceedingly rare and not associated with lymphadenopathy, which precludes the other options.

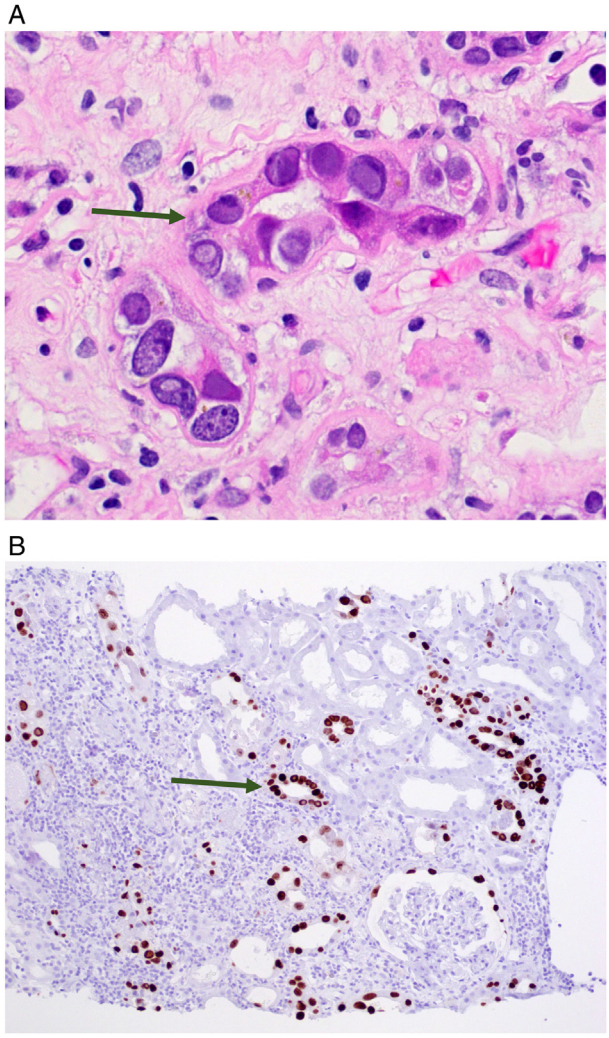

Figure 2. Example of BK (polyoma) tubular viral inclusions in native kidney specimen with history of lung transplantation. (A) Light microscopy H&E stain showing tubular epithelial cells with intranuclear inclusions (arrow) and enlarged nuclei. Original magnification, ×400. (B) Light microscopy SV40 stain showing intranuclear inclusions of BK virus in tubular epithelial cells (arrow). Original magnification, ×100. Images © 2024 Erika Bracamonte, MD, and are reproduced with permission of the copyright holder.

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Conclusion

A high burden of viral illnesses impacts the global community, and many of these illnesses lead to glomerular and/or tubulointerstitial disease. Viral nephropathies may occur in the setting of acute or chronic infection with varied mechanisms of injury. The mechanism of viral injury drives the kidney pathology and clinical presentation. Whether the viral nephropathy is due to the direct viral infection of kidney parenchymal cells or due to an indirect immune-related phenomenon related to viremia, the mainstay of therapy includes management of viremia or supportive care in instances when no direct antiviral therapy exists. However, because some antiviral therapies are also nephrotoxic, patients with chronic viral illnesses receiving chronic antiviral therapy require careful history and evaluation to determine the underlying cause of kidney dysfunction. Advances in the role of genetics, such as *APOL1* polymorphisms, and in antiviral therapeutics, such as cART and DAA, and in preventative therapies, as with SARS-CoV-2 vaccination, are rapidly changing the landscape of these diseases and their associated kidney manifestations.

Article Information

Authors' Full Names and Academic Degrees: Amy A. Yau, MD, Sangeetha Murugapandian, MD, Ali W. Rizvi, DO, and Anna Gaddy, MD.

Authors' Affiliations: Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio (AAY, AWR); Division of Nephrology, College of Medicine, University of Arizona, Tucson, Arizona (SM); and Division of Nephrology, Medical College of Wisconsin, Milwaukee, Wisconsin (AG).

Address for Correspondence: Amy A. Yau, MD, 1664 Neil Ave 4th Floor, Columbus, OH 43201. Email: amy.yau@osumc.edu

Support: None.

Financial Disclosure: Dr Gaddy receives an annual stipend from MedSpoke for Free Online Access Medical Education (FOAMed) content. The other authors declare that they have no relevant financial interests.

Acknowledgements: Special thanks to Dr. Melanie Hoenig for her support, patience, and friendship.

Peer Review: Received June 15, 2023 in response to an invitation from the journal. Evaluated by 3 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor, the Pathology Editor, and a Deputy Editor. Accepted in revised form June 12, 2024.