Thrombotic Microangiopathy and Other Glomerular Disorders in the HIV-Infected Patient

Derek M. Fine, MD, Agnes B. Fogo, MD,† and Charles E. Alpers, MD‡*

Summary: Various forms of kidney disease have been related directly to human immunodeficiency virus (HIV) viral infection, including HIV-associated nephropathy (HIVAN), immune complex diseases, and thrombotic microangiopathy (TMA). HIVAN and HIV immune complex glomerulonephritides are the most common HIV-specific nephropathies. HIV-associated TMA, although far less common, remains an important consideration. The diagnosis of TMA in HIV, which has a poorly understood pathogenesis, can be suggested by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure, but only definitively diagnosed by kidney biopsy. Not surprisingly, the incidence and prevalence of the HIV-specific entities have declined with the advent of highly active antiretroviral therapy. With this decline, however, other glomerular diseases are of increasing importance in this high-risk population. The differential diagnosis of glomerular disease in an HIV-positive patient is therefore broad. Glomerular diseases seen in this population include classic focal segmental glomerulosclerosis, IgA nephropathy, postinfectious glomerulonephritis, hepatitis B– and C–related glomerulonephritides, and membranous nephropathy. In addition, as the HIV-infected population ages, diabetic and hypertensive nephropathies are likely to become more prevalent. With overlapping presentations of these entities, definitive diagnosis often is difficult, necessitating kidney biopsy. As a consequence of establishing an accurate diagnosis, improved patient outcome can best be accomplished through disease-specific intervention.
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Kidney disease in human immunodeficiency virus (HIV)-infected patients has been recognized since the early years of the epidemic.[1,2] Various forms of disease directly related to the viral infection have been described including HIV-associated nephropathy (HIVAN), immune complex diseases, and thrombotic microangiopathy (TMA).[3] HIV-associated nephropathy and HIV immune complex glomerulonephritides, discussed elsewhere in this issue, are the most common HIV-associated nephropathies. HIV-associated TMA, although far less common, remains an important consideration. Not surprisingly, each of these entities is on the decline with the advent of highly active antiretroviral therapy (ART).[4-7] Therefore, with declining rates of HIV-specific nephropathies in the context of ART use, other glomerular diseases may be emerging as more important entities in this population. The differential diagnosis of clinically suspected glomerular disease in an HIV-infected patient is therefore broad. Classic focal segmental glomerulosclerosis (FSGS) is an important consideration among black patients,[5] who now comprise an increasing proportion of the HIV population.[8] As the HIV-infected population

*Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.
†Department of Pathology, Vanderbilt University School of Medicine, Nashville, TN.
‡Department of Pathology, University of Washington Medical Center, Seattle, WA.
Dr. Fine has received speaking honoraria and consulting fees from GlaxoSmithKline.
Address reprint requests to Derek M. Fine, MD, Division of Nephrology, 1830 East Monument St, Suite 416, Baltimore, MD 21205. E-mail: dfine1@jhmi.edu
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ages, diabetic and hypertensive nephropathies are likely to become more prevalent. Monoclonal gammopathy and associated diseases also may become more common as this population ages. In addition, HIV-infected persons have a high prevalence of other risk factors for renal disease including hepatitis C virus (HCV) infection.

In this article we discuss HIV-associated TMA and other glomerular lesions that are not specific to HIV infection, but that must be considered in the differential diagnosis of an HIV-infected patient presenting with renal dysfunction.

HIV-ASSOCIATED THROMBOTIC MICROANGIOPATHY

Thrombotic microangiopathy is a nonspecific term describing a constellation of pathologic alterations in the context of a variety of diseases and initiating events (Table 1).[9,10] The TMAs most often are characterized by microangiopathic hemolytic anemia, thrombocytopenia, high lactate dehydrogenase (LDH) levels, microvascular thrombosis, and multiorgan dysfunction, but the particular constellation of features varies considerably in individual patients. These disorders often have kidney involvement, with acute kidney injury and variable levels of proteinuria and hematuria. TMA involving the kidney in patients with HIV infection, either thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS), is relatively uncommon. This entity was first described in an acquired immune deficiency syndrome (AIDS) patient by Boccia et al[11] in 1984. Since then, TMA has been widely reported in HIV-infected people as the most common microvascular injury associated with HIV infection.[12-26]

Table 1. Causes of Thrombotic Microangiopathy

HIV infection
Hemolytic–uremic syndrome
Thrombotic thrombocytopenic purpura
Malignant hypertension
Disseminated intravascular coagulation
Eclampsia/preeclampsia
Scleroderma
Antiphospholipid antibody syndrome
Postpartum renal failure
Oral contraceptives
Infections
Malignancy
Allograft rejection
Systemic lupus erythematosus
Hereditary plasma defects
Radiation
Medications/toxins

The presentation of TTP, a severe manifestation of TMA, is characterized by a pentad of findings with variable expression: fever, neurologic dysfunction, thrombocytopenia, microangiopathic hemolytic anemia, and renal failure. This constellation is differentiated in most of the literature from HUS by the presence of neurologic symptoms and fever; however, the distinction between these diagnoses is not always straightforward because of significant overlap.[10] Patients with TMA involving the kidney typically present with acute renal failure, which often is rapidly progressive with variable levels of proteinuria and hematuria. Although the presence of microangiopathic hemolytic anemia and thrombocytopenia are suggestive of TMA, the diagnosis is difficult to establish without kidney biopsy because there may be significant overlap with other renal diseases seen in the context of HIV infection. Table 2 lists several of the glomerular diseases that may present similarly with combinations of acute renal failure, proteinuria, and/or hematuria.

Much of our knowledge of TMA in patients with HIV is based on cases reported in the pre-ART era in patients with advanced HIV disease. These patients frequently had ambiguous presentations for which alternate explanations were possible. For example, neurologic symptoms and fever are not infrequent findings in end-stage AIDS, and may be seen in those with HUS as well as TTP. We will therefore use the umbrella term HIV-associated TMA to include both HUS, TTP, and overlap settings. A further difficulty that complicates our ability to understand the underlying cause of TMA is that the injury has multifactorial etiologies and may not always be attributable directly to HIV infection. This is typified by the first described case of

Table 2. Glomerular Disease in HIV-Infected Patients

HIV-related
HIV-associated nephropathy
HIV-related immune complex disease
Immune complex–mediated GN
IgA nephropathy
Mixed sclerotic/inflammatory
Lupus-like disease
Thrombotic microangiopathy
Non–HIV-related
Classic FSGS
Diabetic nephropathy
Membranoproliferative GN (± cryoglobulinemic GN)
Postinfectious GN
Hypertensive nephrosclerosis
Membranous nephropathy
IgA nephropathy
Amyloidosis
Minimal change disease

NOTE. Order based on frequency of lesions as reported by Berliner et al.[4]
Abbreviation: GN, glomerulonephritis.

TMA in an HIV-infected patient. This patient had active and widespread Kaposi's sarcoma, had just received chemotherapy, and died from staphylococcal sepsis shortly after diagnosis with TMA.[11]

Epidemiology of HIV-Associated TMA

The prevalence of HIV-associated TMA is uncertain. Some data suggest that HIV-associated TMA is an underrecognized clinical entity. The diagnosis can be difficult, particularly if the clinical findings largely are limited to the kidney. In these cases it can be recognized only by characteristic histopathologic findings on kidney biopsy. However, there is reluctance by many to perform kidney biopsies in patients with HIV infection. A multicenter autopsy study showed TMA in 15 of 214 patients (7%) whose deaths were attributable to AIDS.[27] A French study of 92 HIV-infected patients, 60 of whom underwent biopsy, found that the most common cause of acute renal failure was HUS.[22] Interestingly, HIV-associated TMA was even more prevalent than HIV-associated nephropathy and involved 32 of the 92 patients, with biopsy-proven diagnosis in 26. Both of these studies included patients predominantly from the pre-ART era. However, other biopsy series have failed to document similar figures for the prevalence of HIV-associated TMA, despite spanning both pre-ART and ART eras. For example, in 2 independent series of biopsied patients (199 biopsies total), no cases of TMA were reported.[4,28] However, it is difficult to infer prevalence from biopsy studies because of the significant selection bias combined with the frequent reluctance of physicians to perform kidney biopsies in HIV-infected patients. In a retrospective study assessing pre-ART and ART era prevalence, 1.4% (17 of 1,223) of AIDS patients were diagnosed with TMA in the pre-ART era, whereas no cases developed in 347 patients evaluated over a 4-year period in the ART era.[6] Therefore, the magnitude of the problem, although not negligible, likely is smaller than suggested by the earlier studies.[22,27]

Clinical Features of HIV-Associated Renal TMA

Review of published case reports and series reveals that no clinical feature specifies the diagnosis of this entity in HIV patients. The presence of a microangiopathic hemolytic anemia, thrombocytopenia, and high LDH level in the presence of acute renal failure suggests the diagnosis. TMA appears to occur in those with untreated infection and advanced disease as indicated by low CD4 counts. However, TMA also has been described as a first manifestation of HIV infection.[17,23,26] Varying levels of proteinuria are seen including, rarely, nephrotic range,[23,29] although high levels are uncommon and may help differentiate this from other disorders, such as HIVAN. Kidney biopsy is required to establish a diagnosis of TMA, although low platelet counts may preclude safe performance of this procedure.

The study by Peraldi et al[22] presents the largest series of HIV patients with hemolytic uremic syndrome. The high prevalence seen in this study has not been duplicated elsewhere, suggesting that these findings may not be applicable to current populations. This population was very ill with advanced HIV disease (mean CD4,

43/mm^3; range, 1-360/mm^3) and multiple opportunistic infections. No mention was made of viral loads or antiretroviral use in the subset of patients with TMA. In the overall study population, 88% were on at least 1 antiretroviral drug, but only 12% were on 3 drugs, and only 5% were on a triple drug regimen that included a protease inhibitor. Interestingly, 12 of the 26 biopsied patients had active cytomegalovirus (CMV) viremia with CMV inclusions in endothelial cells, suggesting a potential pathogenic role of CMV in the process.[30] The mean serum creatinine level at presentation was 4.2 mg/dL (range, 2-15 mg/dL), and proteinuria levels were variable with a median level of 1.76 g/24 h (range, 0-4.5 g/24 h).[22] Seven patients required dialysis within 2 days of development of acute renal failure. The median platelet count was 77,000/mm^3 (range, 10,000-160,000 mm^3). Evidence of a microangiopathic hemolytic anemia was seen in 20 of 26 biopsied patients. High LDH levels and low haptoglobin levels were the rule. All patients had normal coagulation studies.

The clinical presentation of HUS and TTP in the general population has similar features. The many case reports of this entity in HIV have parameters in similar ranges to those described by Peraldi et al,[22] most notably the frequent presence of advanced AIDS.[6,31]

Pathologic Findings in HIV-Associated TMA

The pathologic features of HIV-associated TMA are not different from those of TTP and HUS seen in the general population. Typical pathologic findings of acute lesions include occlusive thrombi in glomeruli and small arteries and arterioles, detachment of glomerular endothelial cells from the basement membrane, mesangiolysis, and widening of the subendothelial space of glomerular capillaries by electron-lucent material presumed to be derived from plasma (Fig. 1). In the chronic phase, reduplication of capillary basement membranes occurs as a consequence of either new basement membrane synthesis and/or "splitting" of the capillary walls by interposed cells and/or insudated plasma and plasma proteins.[32] Segmental sclerosis in a secondary pattern may develop, along with tubular atrophy and interstitial fibrosis. In the chronic phase, arterioles and arteries show intimal reduplication, so-called *onion-skinning*. Microvascular thrombi may contain red cell fragments, which can be highlighted with trichrome or phosphotungstic acid–hematoxylin stains. With severe vascular lesions, cortical necrosis may develop.

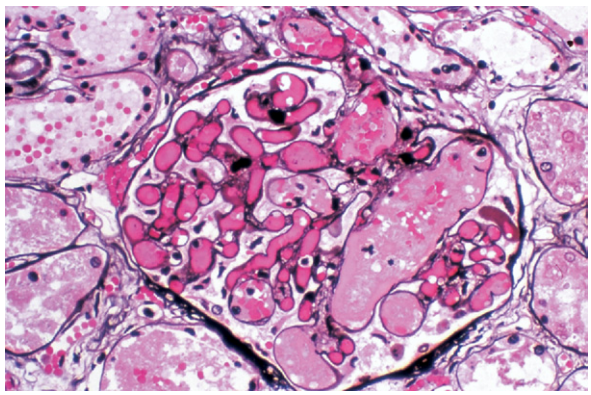

Figure 1. Glomerulus from an HIV-infected patient who died with a clinical diagnosis of TTP. There are thrombi occluding glomerular capillaries and a hilar arteriole, and dilatation of some glomerular capillary loops consequent to mesangiolysis.

Immunofluorescence studies show no specific staining for deposits of immunoglobulins or complement components; stains for fibrin/fibrinogen may detect intravascular thrombi when present.

Of note, in HIV-infected patients, regardless of whether any renal disease is present or not, tubuloreticular inclusions may be present in the endothelial cell cytoplasm throughout the body.[33] These peculiar modifications of endoplasmic reticulum are "footprints" of high levels of circulating interferon-alfa, and appear to be less numerous in biopsies performed in the ART era.[34]

Pathogenesis of HIV-Associated TMA

The thrombotic microangiopathies result from injury to the endothelial lining of the microvasculature. Exposure to phenotypically altered endothelium or subendothelial matrix consequent to this injury is thought to cause platelet activation and aggregation, in turn activating the plasma coagulation cascade and causing local thrombosis.[9,10,32] The kidney, with its large

microvascular surface area, is an organ particularly susceptible to TMA.[32,35] Whether endothelial cells are injured directly by toxins, shear stress, vasoactive factors, or immune/inflammatory injury, their response produces a microenvironment in which coagulation and intravascular thrombosis are favored. This injury is unrelated to immune-complex deposition in glomeruli or blood vessels.[36]

The pathogenesis of TMA in HIV, although clearly involving endothelial injury, is not clearly understood.[36] The pathogenesis of TMA occurring outside the setting of HIV infection is multifactorial, and some of the same mechanisms likely are activated when HIV patients develop TMA. Some well-described mediators include products of bacterial infection (verotoxins such as Shiga toxin from *Shigella dysenteriae* and Shiga-like toxins from *Escherichia coli* O:157, and bacterial and viral neuraminidases), certain drugs (eg, calcineurin inhibitors and antagonists of vascular endothelial growth factor), radiation, complement dysregulation, abnormalities in vWF activity (ADAMTS-13 deficiency, inherited or acquired), and circulating antiphospholipid antibodies.[9,10,37,38] Certain disease settings also predispose patients to TMA, including malignant hypertension, scleroderma, cancers, and preeclampsia. A small minority of affected individuals have familial thrombotic microangiopathies, predisposing them to relapsing episodes of TMA. In a significant number of individuals with idiopathic TMA, the pathogenesis remains undetermined. TTP most commonly is the result of circulating antibodies to or deficiency of ADAMTS 13, a von Willebrand factor–cleaving protease, but overlap with a HUS-like presentation occurs.[10,39,40]

The mechanism by which HIV infection is linked to TMA almost certainly is indirect. Although there is evidence that podocytes and renal tubular epithelial cells can be infected with HIV in vivo,[41-44] direct infection of renal endothelial cells has not been shown. Furthermore, the renal microvasculature lacks expression of CD4 and other co-receptors (eg, CCR5 and CXCR4) that mediate HIV infection of leukocytes.[36,45,46]

Therefore, other mechanisms must be considered. Intact HIV virions and peptide subunits have been shown to cause apoptosis in human umbilical vein endothelial cell and human microvascular endothelial cell cultures[47,48] and other data suggest that the HIV envelope protein gp120 can induce expression of the procoagulant tissue factor in human arterial smooth muscle cells.[49] These suggestive findings have not yet led to more conclusive demonstration of prothrombotic effects in vivo, and hence their potential role in the pathogenesis of HIV-associated TMA remains poorly understood. This makes it unlikely that renal TMA is the result of a direct interaction of HIV virions and microvascular endothelium.

Based on the frequent finding of antiphospholipid antibodies in blood samples of asymptomatic HIV-infected patients,[50] some researchers have hypothesized a role for circulating antiphospholipid autoantibodies in initiating this injury, although most of these individuals lack clinically relevant thrombotic events.[51,52]

Although there are several animal models of TMA, the only one associated with HIV is that in the macaque. Macaques infected with the HIV-2 virus (287 clone), a strain that can cause AIDS in these animals within 6 to 12 months,[53] develop peripheral CD4 decreases and have an approximate 25% incidence of TMA within 1 month of infection.[54] The animals with TMA develop thromboses in both renal and extrarenal sites, and have histopathologic findings remarkably similar to those of human TMA. Endothelial and vascular smooth muscle cell injury was seen that resembles apoptosis, in some but not all features. Widespread labeling of the injured tissues was seen by terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling staining, a histologic procedure highly but not absolutely specific for apoptosis. Although other markers of apoptosis also are present,[55] the features seen in this model have been distinguished from apoptosis.[36] Because of the striking demonstration of discrete areas of injury marked by terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling positivity, which frequently were glomerular, vascular, and perivascular in location, the investigators referred to this injury as *tunelosis*, which appears to be a unique form of cellular injury.[36] TMA with similar phenotypic characteristics

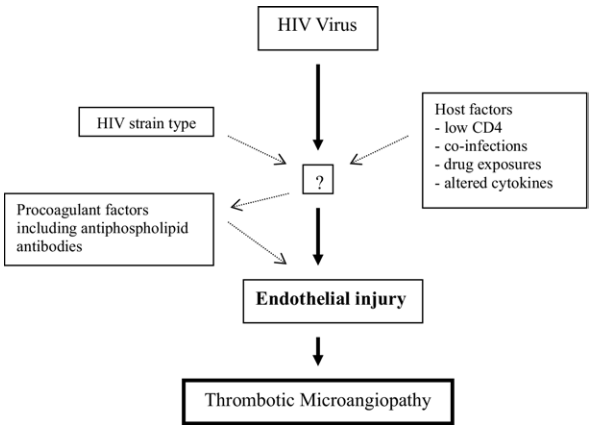

Figure 2. Possible pathogenesis pathway of HIV-associated TMA. Central to the pathogenesis is endothelial injury that is related indirectly to the presence of HIV virus. Mechanisms (shown as "?") are unknown and likely are influenced by multiple factors.

has yet to be shown in human HIV-associated TMA, and mechanistic relationships suggested by this model have yet to be developed.[36]

In summary, the TMA of HIV, similar to TMA resulting from other etiologies, appears to occur as a result of endothelial injury, although the mechanisms remain uncertain (Fig. 2). Involvement of the virus itself may be suggested by the significant reduction of this entity seen in the ART era,[6] although a primary role for other unspecified disease processes consequent to HIV infection also are compatible with this observation.

Treatment of HIV-Associated TMA

Unfortunately, treatment options for HIV-associated TMA are limited and not evidence-based because of a lack of controlled trials. As with treatment of TTP and HUS in the non–HIV-infected population, plasmapheresis with plasma exchange has perhaps been the most widely used therapeutic modality. This approach has had only inconsistent success, possibly in part owing to the advanced state of HIV infection in many patients. Plasma exchange was deemed the treatment of choice in one literature review, although still was associated with a mortality of 22%.[31] In the retrospective study by Peraldi et al,[22] 21 patients received plasma infusions and 8 underwent plasma exchange. Eighteen had improvement of renal function and 7 died within 2 months of diagnosis. No details were given regarding the effectiveness of each therapy separately. Corticosteroids, splenectomy, immunoglobulin infusions, and antiplatelet agents also have been used in patients with HIV-related TMA with variable degrees of success.[23,29,56,57]

Because of the possible pathogenic role of HIV itself and evidence that TMA is infrequent in the ART era, it seems reasonable that treatment with ART would be appropriate. As with HIVAN, rapid institution of ART should be pursued while plasmapheresis or another chosen therapy is in place. Consultation with a hematologist is recommended.

NON–HIV-RELATED GLOMERULAR KIDNEY DISEASE

HIV patients are likely to suffer similar non–HIV-related diseases as their age-matched counterparts in the general population, and with effective ART these should be considered in a patient presenting with glomerular disease. They may have similar or overlapping clinical presentations with HIV-specific and other nonspecific diseases and, therefore, biopsy usually is needed to make a definitive diagnosis. Non–HIV-related glomerular diseases likely to occur in HIV-infected patients include classic FSGS, the most common cause of nephrotic syndrome in African Americans, and IgA nephropathy, the most common cause of glomerulonephritis in renal biopsy series worldwide. Indeed, both of these entities have been seen in biopsy series.[4,5,28] Even minimal change disease may occur in HIV patients.[4,5,21,28,58] HCV-related kidney disease, often manifesting as cryoglobulinemic glomerulonephritis, may occur in those with HCV co-infection[59] and is discussed in detail elsewhere in this issue. Membranous nephropathy, a common cause of nephrotic syndrome in the general adult population that has been associated with hepatitis B, also can be observed in the HIV population.[4,5,28] Of increasing importance in this aging population are hypertensive nephrosclerosis and diabetic nephropathy.[5,28] Although any glomerular disease that occurs in the general population can be found, other glomerular diseases to consider in HIV-infected patients include postinfectious glomerulonephritis, AA-amyloidosis (in chronic

injection drug users) or AL-amyloidosis (in older patients), lupus nephritis, and membranous nephropathy.

Noncollapsing FSGS and Membranous Nephropathy

The entities of FSGS and membranous nephropathy in the general population have been reviewed elsewhere.[60-62] They are unlikely to present differently in the HIV population. A detailed discussion of these entities is beyond the purview of this article. However, as noted earlier, both these entities have been seen in patients with HIV.[4,5,28] In an inner-city African American cohort, classic noncollapsing FSGS was diagnosed in 34 of 152 (22.4%) patients undergoing a biopsy.[4] Although difficult to distinguish from secondary forms, most cases were believed to be primary in etiology. Classic FSGS in its primary form can present with varying levels of proteinuria and renal failure. Hematuria may occur and hypertension frequently is present. Treatment may range from aggressive blockade of the renin-angiotensin-aldosterone axis to immunosuppression. The use of immunosuppressive agents generally will be reserved for those under suppressive antiretroviral therapy.

Primary membranous nephropathy is less prevalent than FSGS in the HIV population, ranging from 3.3% to 5.6% of biopsied patients.[4,5,28] Those with membranous nephropathy tend to present with higher levels of proteinuria than those with FSGS, usually nephrotic. Hematuria is uncommon. The level of renal failure may vary. Spontaneous remissions occur in approximately one third of cases, whereas a third will have progressive disease. The remainder will have stable function despite persistent proteinuria.[62] Treatment options, as with FSGS, vary and may include immunosuppression. Those with membranous nephropathy are also at increased risk of deep vein and renal vein thromboses.[63]

Diabetic and Hypertensive Renal Disease

As the HIV-infected population ages in the ART era, we are witnessing an increased prevalence of chronic kidney disease (CKD).[64] It is likely that diabetes and hypertension will play an increasingly important etiologic role in CKD in these patients. In the general population, more than 70% of end-stage renal disease is attributable to these disorders.[65] It is not surprising, therefore, that diabetic and hypertensive nephropathies are among the most important non–HIV-related diagnoses in biopsy studies of HIV patients.[4,5,28] These diseases may become more important as the ethnic make-up of the HIV-infected population changes. According to Centers for Disease Control and Prevention data, African Americans now comprise more than 50% of the new cases of HIV and 48% of the current HIV population in the United States.[8] African Americans have a significantly increased risk for both diabetes and hypertension and related renal disease compared with Caucasians.[66,67] The phenotype of renal injury associated with hypertension also differs in African Americans, with more frequent global glomerulosclerosis.[68] This lesion was termed *decompensated benign nephrosclerosis* by Fahr,[69] and is associated with worse prognosis. Aggressive therapy, including angiotensin-converting enzyme (ACE) inhibitors, may be necessary in African Americans to slow progression.[70]

Hypertension, which is estimated to be present in 12% to 21% of the HIV-infected population, is an independent risk factor for mortality in women beginning ART.[71] Ritonavir-boosted lopinavir has been associated with increased risk of hypertension, although the effect appears to mediated through increased body mass index.[72] In addition, antiretrovirals, specifically protease inhibitors, have been suggested to predispose to the development of dysmetabolic syndrome,[73] which can exacerbate adverse effects of both diabetes and hypertension on the kidney. In addition, cocaine use, which is not infrequent in some HIV populations, is a well-described nephrotoxin and avid vasoconstrictor and has been linked to hypertensive renal changes in HIV patients.[74]

Aggressive attempts should be made to modify the risk factors of hypertension, diabetes, and substance abuse, particularly in those with the highest risk. Based on National Kidney Foundation guidelines,[75] the recent Infectious Diseases Society of America (IDSA) guidelines[76] recommend that in patients with CKD, blood

pressure should be controlled to 125/75 mm Hg or lower. Although the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) report recommends a different target of 130/80 mm Hg in the CKD population, the guidelines agree that in those with proteinuria, initial use of ACE inhibitors or angiotensin-receptor blockers is preferred to control blood pressure.[75-77] Indeed, some studies support that doses beyond blood pressure control, or the combination of ACE inhibitor and angiotensin-receptor blockers, may have added beneficial effects on proteinuria and progression.[78,79]

Postinfectious Glomerulonephritis

Postinfectious glomerulonephritis is an important diagnosis because its clinical features have significant overlap with other glomerular diseases. When pre-existing infection is not identified, as often happens, this diagnosis is not considered. Although HIV patients are less prone to infection in the ART era, infection is still more likely than in the population at large. Postinfectious glomerulonephritis must be considered as a cause of glomerular disease in the context of recent infection, and even in the absence of obvious infection. In one biopsy series in HIV patients, postinfectious glomerulonephritis was the primary diagnosis in 4.6% of 152 biopsied patients, the fifth most common diagnosis after HIVAN, classic FSGS, diabetic nephropathy, and membranoproliferative glomerulonephritis.[4] In adults, this disease presents with variable levels of proteinuria, often nephrotic, as well as with hematuria and acute kidney injury.[60-63] In a recent study of 86 adults with postinfectious glomerulonephritis, 76% had greater than 1 g/24 h proteinuria, with 40% in the nephrotic range. Ninety-one percent had hematuria, 20% had gross hematuria, and 18% had red blood cell casts.[63] In adults, complete recovery rates have ranged from 28% to 64%.[60-63] Although high ASO titers and low complement levels may be suggestive of the diagnosis, they frequently are not present. Streptococcal infections cause 17% to 40% of cases in adults, with 12% to 25% related to Staphylococcal infections. Of note, staphylococcal infections may give rise to an IgA-dominant postinfectious glomerulonephritis, diagnosable by typical hump-like deposits on electron microscopy and strong C3 staining.[80,81] It is important to differentiate this entity from IgA nephropathy because treatments and prognoses differ. Interestingly, in large series, 24% to 59% of postinfectious glomerulonephritis cases had no identifiable organism and 7% to 16% had no evidence of preceding infection. Therefore, the absence of a preceding clinically obvious infection does not rule out postinfectious glomerulonephritis as a cause of renal disease.[60-63] Although no specific therapy may be instituted when this diagnosis is made, its presence will preclude other interventions by excluding other diagnoses.

CONCLUSIONS

Identification and definitive diagnosis of HIV-related and unrelated kidney disease is critical to patient management. The HIV population is at high risk for kidney disease and the differential diagnosis is at times vast. Although HIV-specific causes, TMA included, are on the decline, they remain important, and when diagnosed treatment will involve antiretroviral therapy. The diagnosis of TMA, which has a poorly understood pathogenesis, can be suggested by clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. However, with overlapping presentations of other HIV-specific and non–HIV-related glomerular diseases, TMA can be diagnosed definitively only by kidney biopsy. Only accurate diagnosis of the underlying disease can allow appropriate focused management.

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