Glomerular Diseases

Review Article

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Viral Glomerulopathy

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Abstract
Background: The association between viral infections and glomerular diseases, commonly known as "viral glomerulopathies," has been described in various clinical scenarios for decades. Despite advancements in diagnostic tools, it remains challenging to establish a causative link fully. ***Summary:*** Data from mouse models have substantiated clinical observations and implicate direct viral infection in the pathogenesis of viral glomerulopathy, particularly in human immunodeficiency virus-associated nephropathy. In addition to the traditional concept of direct viral effects on kidneys, other factors such as *APOL1* risk alleles can further modify the clinical outcomes or presentations of different viral glomerulopathies. Newly developed antiviral drugs are now applicable to a wider range of patients with lower kidney function and fewer side effects. ***Key Message:*** Efforts focusing on vaccines and antiviral treatments have significantly reduced the incidence of viral glomerulopathies. However, the most recent pandemic caused by severe acute respiratory syndrome coronavirus 2 infection complicated by COVID-associated nephropathy illustrates our susceptibility to novel viruses. Ongoing research is pivotal to deciphering the mechanisms behind viral glomerulopathies and discovering therapeutics in a collaborative approach.

Introduction

Viral glomerulopathies are a group of glomerular diseases associated with systemic viral infections. After acute infection, patients typically develop viral symptoms such as fever and chills, and specific serological tests should be positive to confirm the diagnosis. In addition, detecting viral antigens or antibodies against antigens within kidney tissue by molecular methods is important in the link between virus infection and kidney pathology. Multiple studies have demonstrated the association between human immunodeficiency virus (HIV) and kidney diseases in human and mouse models. Furthermore, antiviral treatments such as antiretroviral therapy (ART) have greatly decreased the incidence of HIV-associated nephropathy (HIVAN). Despite these encouraging successes, there is a risk of emerging and highly contagious viruses leading to severe outbreaks if our bodies have not yet established immunity against them. The most recent example is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, also known as the COVID-19 pandemic. At the beginning of this pandemic, we were devastated to see patients with COVID-19 develop severe acute kidney injury (AKI) requiring kidney replacement therapy (KRT). Although the exact pathogenesis of COVID-associated nephropathy remains unclear, it highlights the need for further research focusing on viral glomerulopathy and early recognition by practicing clinicians. Here, we will review the mechanisms of viral glomerulopathy and common viral glomerulopathies

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Table 1. Viral infections known to cause glomerular diseases

Virus	Associated glomerular disease
Hepatitis B	MN FSGS IgAN
Hepatitis C	Mixed cryoglobulinemia MN
SARS-CoV-2	Collapsing glomerulopathy
HIV	HIVAN (collapsing form of FSGS) Immune complex-mediated glomerular disease

associated with HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), and SARS-CoV-2 infection, as summarized in Table 1.

HIV-Related Kidney Disease

The spectrum of HIV-related kidney disease has changed considerably since the first reported case of HIVAN in 1984 [1, 2]. Apart from HIVAN, HIV-related kidney diseases now encompass other pathological processes, including immune complex-mediated glomerular disease in the setting of HIV, thrombotic microangiopathy, and nephrotoxicity from combined ART [3]. Early studies suggest that kidney tubular cells and glomeruli can be the direct reservoirs of HIV [4–6]. An example of this is in kidney transplantation, where a donor-derived HIV strain was detected in an HIV-positive kidney transplant recipient after kidney transplantation, supporting the concept of local infection inside the kidneys [7]. Mechanistically, our group and others have demonstrated the potential pathological roles of HIV infection in podocyte dedifferentiation and severe glomerulosclerosis by using transgenic mice models in which podocytes overexpress proteins encoded by HIV [8, 9]. Most recently, the association between worse clinical outcomes and genetic predispositions, including apolipoprotein L1 (*APOL1*) risk alleles, further elucidates the underlying pathophysiology of HIV-related kidney diseases [10].

HIV-Associated Nephropathy

HIVAN typically occurs in patients with advanced HIV infection with low CD4 cell counts (less than 200 cells/mm^3). Patients usually present with nephrotic proteinuria, suggestive of podocyte pathology, and could develop a rapid decline of kidney function requiring KRT [11]. HIVAN is histologically characterized by collapsing focal segmental glomerulosclerosis (FSGS) and proliferating glomerular epithelial cells (often referred to as "pseudocrescents") [12]. Microcystic tubular dilatation is often seen in the tubulointerstitium. Activated interferon signals can trigger tubuloreticular inclusions formation in the endothelium, and effacement of podocyte foot processes are important diagnostic clues by electron microscopy. Tubuloreticular inclusions are not pathognomic for HIVAN, as they are seen in other viral glomerulopathies and lupus nephritis [12]. It is also important to note that not all patients with HIV and nephrotic proteinuria are diagnosed with HIVAN. Atta et al. [13] showed that 47% of patients with nephrotic range proteinuria had an alternative diagnosis based on kidney biopsies in their cohort study. On the contrary, HIVAN could also manifest as subnephrotic range proteinuria [11, 13]. Therefore, a kidney biopsy remains necessary to establish the etiology of kidney disease in many persons with HIV.

In the past decade, the link between *APOL1* risk alleles and the development of kidney diseases has been a breakthrough finding in the field. For example, patients with *APOL1* risk alleles have a 29-fold greater risk of developing HIVAN, commonly seen in people of African descent [10]. The exact mechanism on how *APOL1* risk alleles cause kidney disease is still under investigation. Current data suggest that the *APOL1* risk alleles (G1/G2) could lead to mitochondrial dysfunction [14]. Recently published data on inaxaplin, a small molecule that targets *APOL1*, were efficacious in reducing proteinuria [15].

HIV and Diabetic Kidney Disease

HIV is known to aggravate pre-existing diabetic kidney disease in patients, independent of other risk factors such as ethnicity and genetic background [14, 16]. In a mouse model of diabetic mice, overexpression of HIV transgenes exacerbates kidney injury [17]. Most recently, Feng et al. [18] further reported that the reduction in sirtuin-1 deacetylase contributes to the progression of diabetic kidney disease with HIV infection.

Similar to other proteinuric diseases, patients with HIVAN should be treated with agents that block the renal-angiotensin system (RAAS), such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, as long as there are no contraindications [19]. Wei et al. [20] showed improved long-term kidney survival with RAAS blockade in patients with HIVAN, independent of nephrotic status, ART exposure, low CD4 lymphocyte count, or moderate to severe chronic interstitial changes.

Immune Complex-Mediated Glomerular Disease in the Setting of HIV

Another HIV-related kidney disease is an immune complex-mediated glomerular disease in the setting of HIV [3]. IgA nephropathy (IgAN), membranoproliferative glomerulonephritis (MPGN), and lupus-like glomerulonephritis have all been described in HIV patients as well [21–23]. The etiology of immune complex-mediated glomerular disease in the setting of HIV is likely multifactorial, including genetic predisposition, host-pathogen interactions, and environmental factors [24]. Unlike HIVAN, the immune complex-mediated glomerular disease is not directly related to the degree of systemic viral load but rather an immunological phenomenon. This has become the more common cause of glomerulopathy in patients with HIV in the ART era due to the effective suppression of the viral load [21, 25]. Mechanistically, elevated levels of immunoglobins (IgA, IgG, and IgM) could bind to HIV antigens (gp120, gp41, and p24) and subsequently form immune complexes. Kimmel et al. [22] reported circulating immune complexes composed of anti-HIV IgG and IgM reacting with gp41 antigen and p24 antigen, respectively, in 2 patients with HIV and IgAN. Positive IgM, IgG, IgA, C3, and C1q are commonly seen by immunofluorescence staining. Electron-dense deposits can be subendothelial, subepithelial, intramembranous, or mesangial. It is important to note that patients can have concurrent pathologic features of immune complex-mediated glomerular disease in the setting of HIV and HIVAN [25].

Due to its heterogeneous presentation, patients diagnosed with the immune complex-mediated glomerular disease in the setting of HIV can present with proteinuria, hematuria, or AKI. Compared to HIVAN, only about one-third of patients may progress to end-stage kidney disease (ESKD) at 2 years of diagnosis [25]. The role of ART is unclear given the heterogenous pathology associated with immune complex-mediated glomerular disease in the setting of HIV and the lack of well-designed, randomized trials. In a study from South Africa, ART was not associated with kidney function stabilization and proteinuria reduction, though the study showed improved mortality in patients at a 12-month follow-up [26]. Furthermore, ART initiation did not mitigate the progression to ESKD and the need for KRT in patients with the immune complex-mediated glomerular disease [25, 27]. Nevertheless, the renoprotective effects of RAAS blockade with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker were consistent and delayed KRT initiation [27].

COVID-19-Associated Kidney Disease

During the first wave of the COVID-19 pandemic in 2020, multiple meta-analyses and specific population studies from discrete health systems estimated that COVID-19-associated AKI occurred in one-third or more hospitalized COVID-19 patients [28–31]. COVID-19 patients with AKI demonstrated higher mortality rates (approximately 50% vs. 8% among those without AKI). Moreover, among survivors with AKI, 35% have not regained their baseline kidney function [30]. The causal factors of AKI associated with COVID-19 have not been conclusively determined, largely due to inconsistent evidence of viral particles in kidney biopsies. In order to infect host cells, the spike protein of SARS-CoV-2 has to bind to the angiotensin-converting enzyme 2 (ACE2) expressed on cell surfaces, which is subsequently facilitated by proteolytic cleavage via transmembrane protease, serine 2. Similar to lungs, kidney tubules highly express ACE2 acting as a receptor binding to SARS-CoV-2 on the apical side of proximal tubules and theoretically would allow viral entry from the urinary space. However, whether SARS-CoV-2 can be filtered through the glomerular filtration barrier is still unclear. If it is filtered through the glomerular filtration barrier, the discordant distribution of ACE2 (mainly proximal tubules) and transmembrane protease, serine 2 (distal tubules) based on the single-cell data [32] raised further uncertainty of direct uptake by the tubular cells. Despite a seemingly plausible mechanism on how SARS-CoV-2 could directly infect kidney tissues, examination of kidney biopsies suggests that cytokine-mediated effects and immune responses, rather than the direct viral infection, is likely the major pathogenesis. In our institution, we reported a kidney biopsy showing collapsing glomerulopathy in a COVID-19 patient. SARS-CoV-2 RNA in situ hybridization staining was negative for COVID-19 in the kidney, whereas the staining in the lung was positive (Fig. 1) [33]. In a study of native and allograft kidney biopsies [34], the authors did not find evidence of SARS-CoV-2 by various methods, including in situ hybridization, immunohistochemistry, and electron microscopy. Similarly, Sharma et al. [35] reported that among biopsies of 10 patients hospitalized with COVID-19 and AKI, there was no evidence of SARS-CoV-2 in tissue samples.

Histologically, acute tubular injuries were the most common finding in kidney biopsies of patients with COVID-19 and AKI [34, 35], whereas collapsing glomerulopathy was the most common glomerular pathology [34, 36, 37]. While the direct mechanism of action has not been elicited, the conditions have resembled HIVAN, which is

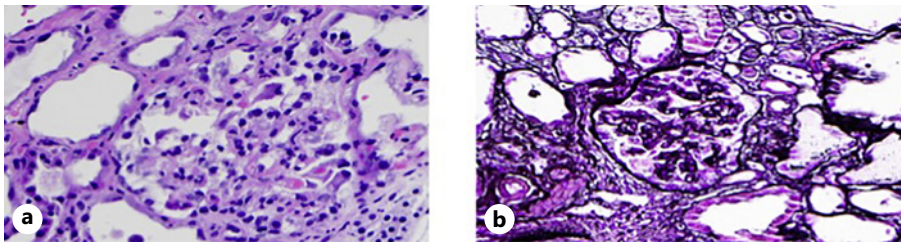

Fig. 1. Collapsing glomerulopathy from a patient with coronavirus disease 2019 (COVID-19) infection. **a** Hematoxylin-eosin (HE) staining (original magnification, ×400). **b** Jones methenamine silver staining (original magnification, ×200). Permission obtained from original publisher [33].

known to occur among patients carrying high-risk *APOL1* alleles [36]. Therefore, it was postulated that the cytokine storm following COVID-19 infection might trigger collapsing glomerulopathy in patients with high-risk *APOL1* alleles [37]. This hypothesis was supported by a case series of 6 patients of African descent. Each patient presented with COVID-19 infection, nephrotic range proteinuria, and AKI, and had undergone a kidney biopsy (five native and one transplant), demonstrating either podocytopathy, collapsing glomerulopathy, or both. Three out of the 6 patients had genetic testing revealing high-risk *APOL1* alleles [36]. Three out of the 6 patients had genetic testing revealing high-risk *APOL1* alleles [36]. Empiric corticosteroid has been used to treat some patients with collapsing FSGS associated with high-risk *APOL1* alleles [38]. However, concerns about nosocomial infection [36] and poor responses to corticosteroids highlight the need for more effective agents.

An additional avenue of ongoing research is the impact of COVID-19 on patients with existing glomerular disease. COVID-19 may provoke adaptive immune responses and subsequently exacerbates immune-mediated glomerular diseases like membranous nephropathy (MN), lupus nephritis, and anti-glomerular basement membrane (anti-GBM) disease [34]. The International Registry of COVID-19 infection in GN (IRoc-GN) was established at the outset of the pandemic to track the short- and long-term impacts of COVID-19 on patients with GN. A study published from that data did not find any differences in mortality and incidence of AKI between patients diagnosed with COVID and a previous history of GN versus patients with COVID only. The main predictor of AKI was pre-COVID-19 eGFR in both populations. However, the rate of incomplete kidney recovery was higher in patients with GN [28].

Lastly, much of the literature had focused on patient populations diagnosed with COVID-19 during the first wave of the pandemic, generally between March and June 2020, when hospitalizations were the highest. There are now proven useful antiviral agents, vaccinations, as well the emergence of less severe but highly transmissible strains. For example, in early 2021, we, along with others, noticed some patients developed either relapsed or developed GN after receiving the SARS-CoV-2 mRNA vaccination [39, 40]. However, the most recent data from the Swiss adult population did not show such an association between the incidence of new-onset GN after vaccination [41]. Meanwhile, increased population immunity due to vaccination and/or previous infection against SARS-CoV-2 would presumably mitigate the incidence of collapsing FSGS.

HCV Immune Complex Glomerulonephritis

The most common glomerular disease associated with HCV is MPGN due to the presence of mixed cryoglobulinemia [42, 43]. MN has also been described, but the causative relationship is relatively unclear [44, 45]. In rare cases, hepatitis C can cause ANCA-associated GN [46]. Mixed cryoglobulinemia is associated with HCV infection in about 10–70% of patients [47] and usually presents as type 2 (polyclonal IgG and monoclonal IgM) and rarely type 3 (polyclonal IgG and IgM) cryoglobulinemia. If present, circulating cryoglobulins form immune complexes and deposit systemically. Mesangium and glomerular capillary depositions result in membranoproliferative GN characterized by a "tram tracking" appearance [48]. Granular deposits of IgG, IgM, and C3 are commonly seen in the mesangium by immunofluorescence, as well as subendothelial immune deposits by electron microscopy. C4, CH50, and C1q are typically low, while C3 can be normal or slightly decreased in the serum [49, 50].

For HCV-related glomerulopathy, pegylated interferon and ribavirin used to be the first-line treatment for chronic HCV infection. Early data suggested the renoprotective benefits of using these agents for proteinuria reduction [51, 52] or stabilization of serum creatinine [53]. However, ribavirin is associated with hemolytic anemia that could be exacerbated by reduced eGFR, therefore limiting its use in patients with chronic kidney disease [54]. Newer direct-acting antiviral agents (DAAs) demonstrated substantially

better clinical, immunological, and sustained viral response and are well-tolerated in patients with reduced eGFR [55, 56]. Therefore, DAAs should be recommended for patients with HCV-associated glomerulopathy [57]. For instance, sofosbuvir-based regimens are recommended for patients with all stages of kidney dysfunction, including ESKD requiring hemodialysis. Immunosuppressive agents, including corticosteroids, rituximab, and cyclophosphamide, have all been used in severe cases of cryoglobulinemia characterized by MPGN, neuropathy, and extensive skin disease. In patients with nephrotic syndrome or rapidly progressive kidney failure, concurrent therapy with immunosuppressive agents and DAAs or sequential therapy of immunosuppressive agents with or without plasmapheresis followed by antiviral therapy is recommended [57]. Given the overt production of cryoglobulins, rituximab is recommended as the first-line immunosuppressant per the 2022 KDIGO guidelines. In a prospective single-center study, 31 patients with mixed cryoglobulinemia (16 patients with MPGN) were treated with rituximab and followed for a mean of 72 months. Rituximab was associated with significant improvement in serum creatinine and proteinuria and no clinically relevant side effects [58].

HBV-Associated Kidney Disease

MN is the most common glomerular pathology associated with chronic HBV infection, followed by MPGN, FSGS, and IgAN [59, 60]. In rare cases, hepatitis B, like hepatitis C, can cause ANCA-associated GN [61]. HBV-associated MN is characterized by thickened glomerular basement membranes with a characteristic "spike" pattern visible on light microscopy, which are immune complexes deposits by hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-Hbe). Diagnosing the association between HBV infection and MN might be clinically challenging, given that confirmatory techniques are not widely available. Therefore, it is reasonable to presume HBV-associated MN in patients with positive hepatitis B surface antigen (HBsAg). In addition, unlike primary MN, the prevalence of anti-phospholipase A2 receptor antibodies (anti-PLA2R) is relatively low in HBV-associated MN. However, in a cohort of Chinese patients, 64% of kidney biopsy samples were positive for anti-PLA2R staining [62].

In the endemic area where vaccination against HBV is unavailable, HBV-associated kidney diseases are mostly seen in children with a relatively benign course and possible spontaneous resolution [63]. On the contrary, the prognosis in adult patients is usually poor and can be exacerbated by other comorbidities such as hypertension and other concurrent liver diseases. In a Chinese cohort of HBV-associated MN, 29% of patients had progressive kidney failure, and 10% required maintenance dialysis [64]. As such, the updated KDIGO guideline suggests that patients with HBV DNA levels >2,000 IU/mL and glomerulonephritis should receive nucleoside/nucleotide analogs treatment [57]. Immunosuppressive agents may accelerate HBV replication and, therefore, should be avoided.

Future Directions

What have we learned from the COVID-19 pandemic in the past 2 years? We might certainly face new strains of viruses, which may lead to another pandemic, and the lack of treatment for kidney complications continues to threaten our vulnerable patients. In addition, current clinical trials exclude patients with existing kidney diseases, limiting the accessibility to therapeutic options [65]. Thus, understanding the underlying kidney pathobiology of viral infections using novel models such as 3D kidney organoids may facilitate future therapeutic target development [66]. Growing evidence utilizing artificial intelligence [67] and next-generation sequencing technologies such as single-cell analysis [68, 69] may also improve the diagnosis of viral glomerulopathies and prediction of kidney outcomes after viral infections. As nephrologists, we hope to be prepared to encounter the next pandemic with more powerful and effective tools to help our patients.

Conclusions

Viral glomerular disease is a complex, evolving, and changing aspect of clinical and basic nephrology research. However, antiviral drugs for HIV and HCV have substantially mitigated the infection and complications such as viral glomerulopathies. However, further study is needed to elucidate the different therapeutic responses individually and the potential use of biological agents to treat glomerulopathies induced by immunological responses. The discovery of the association between APOL1 risk alleles and HIV-related kidney disease has set a great example of providing a more precision medicine-based approach to patient care. We hope to see more data on this rare but important entity of glomerular diseases in the future.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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