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Collapsing glomerulopathy; a review on current studies

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Abstract

Collapsing glomerulopathy is a rare and serious disease that is characterized by a rapid deterioration of kidney function and heavy proteinuria. This disease is a variant of focal segmental glomerulosclerosis (FSGS). The disease is more serious than other types of FSGS, with high risks of renal failure and poor prognosis. Collapsing glomerulopathy is often resistant to immunosuppressive therapy and can rapidly result in renal failure, making diagnosing and managing this disease an enormous challenge.

Keywords: Collapsing glomerulopathy, Focal segmental glomerulosclerosis, Proteinuria, Podocytes, Human immunodeficiency virus, Tubulointerstitial inflammation, Renal biopsy, Glomerular collapse, Interstitial infiltration

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Introduction

Collapsing glomerulopathy, a focal segmental glomerulosclerosis (FSGS) variant, is an uncommon disease where podocytes undergo alteration and cause collapse of the glomerular tufts (1). This disease presents with a rapid decline in kidney function and proteinuria with multiple potential causes or triggers. It is often detected in patients with massive proteinuria. It has been associated with human immunodeficiency virus (HIV) infection and other viral infections such as parvovirus B19, hepatitis B and C viruses, and cytomegalovirus. This glomerulopathy has also been detected following COVID-19 infection (2,3). The mechanisms underlying collapsing glomerulopathy are not fully understood, and the disease actually has no definitive treatment. In this mini-review, we aimed to study the recent knowledge on this disease.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including collapsing glomerulopathy, focal segmental glomerulosclerosis, proteinuria, podocytes, human immunodeficiency virus, tubulointerstitial inflammation, renal biopsy, glomerular collapse, interstitial infiltration, tubular atrophy, immunofluorescence, electron microscopy and *APOL1* risk alleles.

Key point

The underlying causes of the collapsing variant of FSGS are not fully understood. A combination of genetic predisposition, infections, medication toxicity, autoimmune disturbances, and metabolic abnormalities may contribute to the onset of collapsing glomerulopathy.

Pathologic features of collapsing FSGS

The gold standard diagnostic tool to diagnose collapsing glomerulopathy is renal biopsy. The diagnosis is based on several pathologic features that differentiate collapsing glomerulopathy from other types of FSGS (4). The most prominent pathologic feature, although not invariably present and that typically accompanies collapsing glomerulopathy, is the presence of glomerular hypertrophy and parietal hyperplasia between 2% to 3% of cases.

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According to these highly characteristic features and their often dramatic clinical presentation, the pathologic diagnosis of collapsing glomerulopathy in a patient who meets the criteria is typically straightforward (5,6).

The steps typically involved in the definitive diagnosis of collapsing glomerulopathy;

1. The clinical evaluation helps identify patients with symptoms consistent with collapsing glomerulopathy, such as proteinuria, nephrotic syndrome, hypertension, and renal insufficiency (7).
2. The laboratory evaluation involves the measurement of serum creatinine, urine protein levels, and other metabolic and electrolyte parameters. Collapsing glomerulopathy typically presents with nephrotic range proteinuria, elevated creatinine levels, and dyslipidemia (8).
3. Renal biopsy is the gold standard diagnostic tool for collapsing glomerulopathy. Renal biopsy tissue is examined under light microscopy to identify histological features specific to collapsing glomerulopathy, such as glomerular collapse, podocyte changes, interstitial infiltration, and tubular atrophy (5,9).
4. Immunofluorescence is a technique that helps to identify the deposition of immunoglobulins or complement components in the glomeruli, which may indicate the presence of an immune-mediated process (10).
5. Electron microscopy is a technique that provides a detailed view of the ultrastructure of the kidney. This technique helps to identify structural changes in the glomeruli, particularly podocytes and their foot processes (11,12).

The main features seen on renal biopsy in collapsing glomerulopathy are:

Glomerular collapse

A characteristic feature of this glomerulopathy is the collapsing anatomy of the glomerulus when viewed under the microscope. The capillary loop collapses onto itself with marked enlargement of the glomerular tuft and prominent hyperplasia of the parietal epithelial cells (13,14).

Podocyte changes

Podocyte injury and loss are common in collapsing glomerulopathy, and the glomeruli often have fewer podocyte foot processes, appearing “bloated” and swollen. Additionally, altered podocytes may accumulate in the urinary space of the glomeruli, forming pseudo-crescents, which is a sign of severe podocyte damage (15-17).

Interstitial infiltration

Inflammatory cells, especially macrophages and T cells, frequently infiltrate the area between the tubules, known as the interstitium (18,19).

Tubular atrophy

The characteristic loss of tubular structures adjacent to the glomerulus, typical of severe tubular dysfunction, often leads to progressive proteinuria and raises the potential for subsequent fibrosis (20).

Several other features may be present on renal biopsy examination, including:

1. Glomerular microcysts: Small cysts may develop in the glomeruli of some patients with collapsing glomerulopathy. These microcysts may be present near or in collapsing glomeruli and may contribute to disrupting normal glomerular architecture and function.
2. Glomerular sclerosis: Collapsing glomerulopathy can progress to chronic renal disease with significant glomerular sclerosis and sclerosis of the tubular-interstitial compartment, which involves irreversible damage to the kidney parenchyma (21,22).
3. Tubulointerstitial inflammation: Interstitial inflammation can obliterate the interstitial spaces, resulting in an increase in the interstitial matrix and tubular atrophy. This inflammatory reaction in collapsing glomerulopathy generally shows prominent interstitial mononuclear cell infiltration with evident tubulitis (23,24).
4. Capillary thrombi: In a few cases of collapsing glomerulopathy, recurrent thrombotic microangiopathy can be seen associated with or without hemolytic uremic syndrome (25,26).
5. Hemosiderin deposition: Some patients with collapsing glomerulopathy may deposit hemosiderin pigments consistent with significant hemorrhage in the kidney interstitium, which can imply significant vascular injury (27-29).

Pathogenesis of collapsing glomerulopathy

The pathogenesis of collapsing glomerulopathy begins with podocyte injury, followed by tuft collapse and severe tubulointerstitial inflammation (3). These cells are crucial in regulating the glomerular filtration barrier and are essential in maintaining kidney homeostasis. Podocytes are located in the outer layer of the glomerular basement membrane (5,30,31). Their feet interdigitate named also pedicels, are joined by an intricate network of specialized proteins, including nephrin and podocin, which form a filtration barrier involved in maintaining the glomerular filtration rate (GFR) (32). The underlying mechanisms leading to podocyte alteration and collapse of tufts are not fully understood. However, various factors can initiate these events, including genetic and environmental parameters (33). The genetic factors linked to collapsing glomerulopathy are associated with podocyte function and integrity and the mutations on the MYH9 gene, which encodes for non-muscular myosin heavy chain IIA (NMHC IIA). Mutations in the MYH9 gene can disrupt the podocyte cytoskeleton, leading to podocyte detachment and thereby increasing the risk of developing collapsing glomerulopathy (34-36). Likewise,

APOL1 risk alleles which recognized as a contributing factor to the development of collapsing glomerulopathy in non-HIV cases. Previous studies showed two risk alleles in the *APOL1* gene, which encodes for apolipoprotein L1 (*APOL1*), be associated with an increased risk of collapsing glomerulopathy in people of African descent, typically leading to early-onset progressive kidney disease. It is imperative to remark that having these genetic risks does not mean an individual will definitely develop collapsing glomerulopathy. However, having these genetic risks could increase the probability of developing the disease in the presence of other additional risk factors (37,38). It has been shown that around 70% of African Americans who developed HIV-associated nephropathy and, consequently, collapsing glomerulopathy are carriers of the two high-risk *APOL1* alleles. Environmental factors that have been associated with collapsing glomerulopathy include viral infections, particularly HIV viral replication in podocytes, resulting in both a direct cytopathic effect and the expression of pro-inflammatory cytokines (39-41). It is possible that, the virus directly infects podocytes, causing podocyte injury and dysfunction. Since HIV carries the CD4 and CXCR4 co-receptors, which are also present on the surface of podocytes, forming a binding mechanism for viral entry into podocytes. Additionally, HIV viral proteins, such as Nef, Tat, and Vpr, have been reported to upregulate immune cytokines such as TGF-beta, CCL5, and MCP-1. Then, this condition triggers podocyte damage and inflammation, resulting in podocyte compromise and detachment, promoting inflammation-mediated podocyte apoptosis (42,43).

It should be remembered that HIV is the most well-known virus that infects podocytes through co-receptor-mediated entry. More recent investigations showed that HIV-infected podocytes undergo dynamic cytoskeletal remodeling characterized by reorganization of their actin cytoskeleton, resulting in loss of the podocyte interdigitating foot processes leading to hyperplasia and tuft collapse (44,45).

However, other viruses may also infect podocytes through co-receptor-mediated entry, although their contributions to the pathogenesis of collapsing glomerulopathy are less well-understood. For example, the subtype B of human T-cell leukemia virus (HTLV-1), which is more prevalent in Southwestern Japan, has been suggested to cause glomerulopathy. It infects a wide range of cells, including podocytes, and its entry into these cells depends on the co-receptor CXCR4, similar to HIV (3,46). This culminates in podocyte injury, cytoskeletal loss, and podocyte depletion from the glomerular tuft, similar to what is seen in HIV-associated nephropathy (47). Certain viruses impose significant metabolic stress on the body to limit its immunity and may also lead to kidney damage indirectly. Several viruses like cytomegalovirus, parvovirus B19, and hepatitis C virus, upon affecting the body, could trigger cytokines, reactive oxygen species, and inflammation, which could lead to podocyte stress and degeneration (48,49). Moreover, viral infections could also lead to the generation of immune complexes. These immune complexes can deposit around the glomerulus and trigger inflammation, leading to glomerular injury and subsequent development of collapsing glomerulopathy (50,51). Besides, viral infections could lead to the onset of an autoimmune response that produces autoantibodies that target the podocytes in the glomerulus, resulting in injury and subsequent development of collapsing glomerulopathy (16,52). Recent studies showed Enteroviruses, such as the Coxsackie B virus, can enter podocytes through the integrin-mediated cell adhesion response. This involves the virus binding to integrin receptors on the podocyte's surface and initiating a signal transduction cascade that allows viral entry into the podocyte cell. This results in podocyte injury and contributes to the development of collapsing glomerulopathy. Other viruses, like cytomegalovirus, can infect podocytes through membrane diffusion, where the virus particles fuse with the podocyte cell membrane (53-55). Cytomegalovirus utilizes αVβ3 integrins as its binding receptors. Infected podocytes shall often show features characteristic of collapsing glomerulopathy, such as podocyte hypertrophy, vacuolization, and cytoplasmic swelling. On the other hand, the hepatitis C virus can cause direct cytotoxicity to podocytes, leading to podocyte injury and dysfunction. It triggers oxidative stress and inflammation in podocytes, which drive the development of collapsing glomerulopathy. Moreover, exposure to toxic substances, chemokines, fat-soluble vitamins, and other dietary substances or medications could trigger podocyte changes, leading to a proteolysis cascade and glomerular damage (56,57). Other authors showed nonsteroidal anti-inflammatory drugs, interferon therapy, and bisphosphonates have been implicated in the development of this variant of FSGS. Additionally, an immune system imbalance could contribute to the pathogenesis of collapsing glomerulopathy (3,5). Certain circumstances, like autoimmune diseases, have also been connected to the onset of this disease. Other infrequent factors, like metabolic abnormalities such as hyperlipidemia, hyperglycemia, and hyperphosphatemia, have been implicated in the development of collapsing glomerulopathy and can trigger podocyte stress response. Meanwhile, glomerular hyperfiltration, local inflammation, and oxidative stress experienced by the podocytes due to metabolic aberrations may contribute to podocyte injury (23,58). Similarly, rare factors like cytokines, chemokines, and other inflammatory mediators secreted by renal tubular epithelial cells, circulating immune cells, or infiltrating immune cells in the glomerulus have also been detected as responsible for this glomerulopathy (59-61). Following podocytic hyperplasia and collapse of the tuft, an inflammatory process in the glomeruli will trigger the tubulointerstitial inflammation and further exacerbate the development of this glomerulopathy. The inflammation-

induced injury to the glomeruli causes tubular epithelial cell damage and interstitial fibrosis (3,42,62,63).

Clinical features of collapsing glomerulopathy

Collapsing glomerulopathy is indicated by massive proteinuria, rapid deterioration of renal function, a substantial decline of GFR, and a more rapid progression to end-stage renal disease. The clinical presentation of collapsing glomerulopathy is more severe than other FSGS variants. It is often associated with nephrotic syndrome and hematuria (3,22,64).

Treatment of collapsing glomerulopathy

At present, no definitive treatment for collapsing glomerulopathy exists. Management of collapsing glomerulopathy is generally supportive, consisting of diminishing proteinuria and balancing fluids and electrolytes status. Diminution of proteinuria remains challenging, and the effectiveness of available management strategies is limited. The mega-doses of corticosteroids commonly have limited or no efficiency in treating collapsing glomerulopathy (3-5,62,65-67). Alternative therapies, including cyclosporine, rituximab, tacrolimus, plasmapheresis, and stem cell therapy, necessitate confirmation of their effectiveness. Renal replacement therapy like hemodialysis or renal transplantation may be suggested if the GFR decreases to below 15 mL/min (41,68).

The details of the treatment for collapsing glomerulopathy are the following options:

1. Glucocorticoids, such as prednisone and methylprednisolone, are usually the initial treatment for collapsing glomerulopathy. They suppress the immune system and reduce inflammation by inhibiting pro-inflammatory cytokines. The use of glucocorticoids in collapsing glomerulopathy is based on its effectiveness in idiopathic nephrotic syndrome and FSGS. The response to glucocorticoid therapy often depends on several factors like age, ethnicity, histological classification, and extent of renal fibrosis (3,5,69-72).
2. Immunosuppressive agents, such as cyclosporine or mycophenolate, can be administered along with glucocorticoids to counter chronic inflammation, interstitial fibrosis, and podocyte injury. These agents inhibit the immune system and reduce the immune reaction towards the kidney. They, however, carry greater potential for side effects and must be balanced against the benefits of treatment (50,73,74).
3. Renin-angiotensin system inhibitors or angiotensin receptor blockers are used to control hypertension or proteinuria in collapsing glomerulopathy patients to provide renoprotection and potentially slow disease progression. They help reduce the production of angiotensin II, a potent vasoconstrictor that can promote renal vascular hypertension, inflammation, and proteinuria (75,76).
4. Plasmapheresis is a blood-cleansing procedure that removes circulating immune complexes, cytokines, and toxins to provide clearance of pathogenic immune or molecular factors that potentially cause CKD and also for collapsing glomerulopathy. Plasmapheresis is mainly used in refractory cases where there is no improvement in kidney function despite earlier therapies (64,77-79).
5. Supportive measures like diuretics, correction of anemia and metabolic abnormalities, and other therapies like rituximab and intravenous immunoglobulin may be considered. However, these therapies lack definitive evidence of significant benefit in collapsing glomerulopathy outcomes, and further research is necessary to clarify their efficacy and safety (50,80,81).

Conclusion

The collapsing variant of FSGS is a rare and serious disease. Although much is not known about the pathogenesis of collapsing glomerulopathy, these rare cases of FSGS can often be thought of clinically as a distinct entity because of the rapid decline in renal function and heavy proteinuria. The effectiveness of current treatment options remains limited, and disease recurrence is highly possible with kidney transplantation. Further studies elucidating the underlying mechanisms of this disease are necessary to find therapeutic targets for its treatment.

Authors' contribution

Conceptualization: Azar Baradaran, Sina Neshat.
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Funding acquisition: Sina Neshat.
Investigation: Sina Neshat.
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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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