In the name of GOD

Collapsing FSGS

Dr.R.Abolghasemi
Nephrologist
SBMU
IRAN

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Introduction

- Collapsing FSGS; (collapsing glomerulopathy) characterized by:

1)Segmentally or globally collapsed and sclerotic glomerular capillaries
2)Hyperplasia and hypertrophy of overlying glomerular epithelial cells

- Patients typically present with the nephrotic syndrome.

- In the setting of active HIV infection, the kidney disease is (HIVAN)
- Collapsing FSGS is now increasingly described in patients without HIV, many of whom carry an underlying (*APOL1*) genotype.

Collapsing FSGS

- HIV-associated nephropathy (HIVAN)
- Collapsing FSGS not associated with HIV

HIV-associated nephropathy (HIVAN)

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- HIV-associated nephropathy (HIVAN), the classic kidney disease associated with HIV infection, is a collapsing form of focal segmental glomerulosclerosis (FSGS) accompanied by microcystic tubular dilatation and interstitial inflammation.

- Human immunodeficiency virus (HIV) infection has been associated with (AKI) and (CKD).

The pathogenesis of HIVAN

- The pathogenesis of HIVAN is hypothesized to involve direct infection of kidney epithelial cells by HIV with subsequent expression of HIV genes in a genetically susceptible host.

- The strong associations of HIV with African ancestry and *APOL1* gene polymorphisms illustrate the importance of host genetic factors.

PATHOLOGY of (HIVAN)

- HIVAN is characterized by the collapsing form of FSGS.

- In addition to collapsing FSGS, HIVAN is typically characterized by dilated tubules and significant interstitial inflammation. Tubuloreticular inclusions may also be identified on electron microscopy .

CLINICAL MANIFESTATIONS OF (HIVAN)

In patients with classic HIVAN, the following features are usually present:

- **Advanced HIV disease**
- **Nephrotic-range proteinuria**
- **Rapid decline in kidney function**

CLINICAL MANIFESTATIONS of (HIVAN) Advanced HIV disease

- Patients with HIVAN typically have a CD4 count less than 200 cells/microL.
- In a study of 57 patients with proven HIVAN, approximately one-half of whom were taking antiretroviral therapy (ART), the mean HIV viral load was greater than 30,000 copies/mL, and the mean CD4 cell count was 127 cells/microL
- HIVAN has been reported in patients with acute HIV infection

CLINICAL MANIFESTATIONS of (HIVAN)
Nephrotic-range proteinuria

- In a study of 71 children with HIVAN, 72 percent had nephrotic-range proteinuria at the time of presentation .
- Among 57 patients with HIVAN, for example, mean proteinuria was 4.1 g/day, and only 14 percent of patients had proteinuria less than 1.5 g/day .
- However, patients with HIVAN may have substantially less proteinuria early during the course of their disease These findings suggest that HIVAN should also be considered in patients with lesser degrees of proteinuria.

CLINICAL MANIFESTATIONS of (HIVAN)
Rapid decline in kidney function

- At the time of HIVAN diagnosis, adult patients often have severely reduced kidney function, which is attributed to the rapidly progressive course.
- In two studies of adults with HIVAN, the mean estimated glomerular filtration rates (eGFR) at the time of HIVAN diagnosis were 10 and 20 mL/min per 1.73 m^2
- Children may not have similarly severe kidney dysfunction at the time of presentation.

CLINICAL MANIFESTATIONS of (HIVAN) Other manifestations

- Hematuria, hypertension, and edema, may also be present.
- In three studies of adult and pediatric patients with HIVAN, the following characteristics were observed :
- Hematuria – 45 to 75 percent
- Hypertension – 12 to 26 percent
- Edema – 22 to 59 percent
- In addition, the presence of enlarged, hyperechogenic kidneys on ultrasonography has been reported in more than 50 percent of patients with HIVAN.

Diagnosis of (HIVAN)

- The diagnosis of HIVAN should be suspected in any patient with HIV who presents with nephrotic-range proteinuria and rapidly declining kidney function.
- Our suspicion is particularly high if the patient has a CD4 cell count <200 cells/microL, HIV viremia, and/or has a history of nonadherence to antiretroviral therapy (ART).
- Kidney biopsy is currently the only way to establish a definitive diagnosis of HIVAN

Treatment of (HIVAN)

Our approach to the treatment of HIVAN is as follows:

- All patients with HIV infection should receive ART, regardless of CD4 count. For patients with HIVAN who are not already receiving ART, ART should be initiated as soon as possible.
- Patients with HIVAN who have proteinuria and/or hypertension should be treated with an (ACE) inhibitor or (ARB).
- Patients who have persistent proteinuria in spite of treatment with an ACE inhibitor or ARB may benefit from (SGLT2) inhibitor.
- There is generally no role for routine glucocorticoids in patients with HIVAN.
- In patients whose kidney function is not improving with therapy, the use of glucocorticoids may be considered on a case-by-case basis

Prognosis of (HIVAN)

- The prognosis in patients with HIVAN is poor, even among those treated with ART.

- Many such patients will develop end-stage kidney disease (ESKD)

Collapsing FSGS not associated with HIV

Collapsing FSGS not associated with HIV

- Collapsing focal segmental glomerulosclerosis (collapsing FSGS; also known as collapsing glomerulopathy) is a cause of the nephrotic syndrome that is characterized histologically by segmentally or globally collapsed glomerular capillaries and severe tubulointerstitial disease.
- In the past, collapsing FSGS was most often seen in association with HIV infection but is increasingly recognized in patients without HIV.

Collapsing FSGS not associated with HIV Pathogenesis

- The underlying pathogenic event appears to be a severe insult to the integrity and biology of the glomerular visceral epithelial (podocytes) and parietal epithelial cells.
- This is accompanied by a profound loss of function of the glomerular filtration barrier.
- There may be a genetic predisposition toward collapsing FSGS.
- Black patients with risk polymorphisms in the *APOL1* gene are at increased susceptibility to develop collapsing glomerulopathy

Collapsing FSGS not associated with HIV Etiology

- The majority of cases of collapsing FSGS are idiopathic. However, collapsing FSGS has been reported to occur in association with a growing list of disorders.

- These included a systemic lupus erythematosus–like disorder, hepatitis C virus infection, and multiple myeloma.

Collapsing FSGS not associated with HIV

Title:

Disorders associated with collapsing glomerulopathy^[1]

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Disorder	
Infection	HIV, cytomegalovirus, parvovirus B19, Epstein-Barr virus, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), pulmonary tuberculosis, leishmaniasis, malaria
Autoimmune	Adult Still's disease, systemic lupus erythematosus, mixed connective tissue disorder
Malignancy	Hemophagocytic lymphohistiocytosis, multiple myeloma, acute monoblastic leukemia
Acute glomerular ischemia	Thrombotic microangiopathy, renal infarction, atheroembolism, hydrophilic polymer embolism
Genetic	*APOL1* high-risk alleles, sickle cell disease, mitochondrial disorders (coenzyme Q deficiency), acute myoclonus-renal failure syndrome, Galloway-Mowat syndrome
Drug exposure	Bisphosphonates, interferons (alpha, beta, or gamma), anabolic steroids, calcineurin inhibitors, mTOR inhibitors
Superimposed on other glomerular diseases	IgA nephropathy, diabetic glomerulopathy
Posttransplantation (de novo)	Arteriopathy/thrombotic microangiopathy, acute rejection, viral infection (cytomegalovirus, Epstein-Barr virus, BK polyomavirus)

mTOR: mammalian (mechanistic) target of rapamycin; IgA: immunoglobulin A.

References:

Collapsing FSGS not associated with HIV Etiology:Idiopathic

- Most cases of collapsing FSGS not associated with HIV infection are idiopathic .In one series of 88 patients with collapsing FSGS, 77 percent had idiopathic disease.
- The etiology of idiopathic collapsing FSGS is unknown.
- Circulating factors that may be toxic to the glomerular capillary wall or to glomerular visceral epithelial cells have been reported, but not conclusively identified.
- The recurrence of collapsing FSGS after kidney transplantation also supports the presence of a circulating factor in some of these patients.

Collapsing FSGS not associated with HIV Etiology:Infections

- A number of infections other than HIV infection have been associated with collapsing FSGS.
- These include viral, bacterial, and parasitic diseases such as parvovirus B19 infection, pulmonary tuberculosis,CMV, schistosomiasis, filariasis, falciparum malaria, and SARS-CoV-2 infection.
- Collapsing FSGS in patients infected with SARS-CoV-2 has been termed COVID-19-associated nephropathy (COVAN) to distinguish it from most cases of acute kidney injury in patients with COVID-19, which are characterized by acute tubular injury(ATN)

Collapsing FSGS not associated with HIV Etiology:COVAN

- In one single center series of 23 patients with COVAN, 70 percent were male, (91 percent)were Black, and most had only mild or moderate severity of COVID-19 infection .
- Twenty-two of the 23 patients presented with ATN(approximately 60 percent required dialysis), 17 had nephrotic range proteinuria, and 6 had the nephrotic syndrome.
- Among the 17 patients who were genotyped, 16 (94 percent) had two high-risk alleles for *APOL1*. Despite treatment overall outcomes were poor,. Viral infection of the kidney by SARS-CoV-2 was not detected.
- One proposed mechanism for COVAN involves infection-stimulated activation of the interferon-chemokine pathway, which upregulates expression of the *APOL1* variant gene, leading to disruption of podocyte autophagy, mitochondrial injury, and promotion of glomerular epithelial cell death

Collapsing FSGS not associated with HIV Eiology: Bisphosphonates and other drugs

- An unexpected association has been noted between collapsing FSGS and therapy with the bisphosphonate pamidronate in patients with multiple myeloma or breast cancer who are often treated with high doses .A toxic effect on the glomerular epithelial cell is the mechanism.
- alendronate and zoledronate, have also been associated with collapsing FSGS in rare cases.
- Anabolic steroids and other bodybuilding supplements and the therapeutic use of interferon-alpha, beta, and gamma have all been associated with the development of collapsing FSGS

Collapsing FSGS not associated with HIV Etiology: Autoimmune disorders

- C-FSGS has been observed in patients with SLE.As an example, a retrospective review of kidney biopsies performed in patients with SLE over a seven year period revealed 19 HIV-negative patients with collapsing FSGS
- Most of those identified were Black & were female ,16 of the 19 patients had symptoms of an active lupus flare at the time of biopsy. nephrotic-range proteinuria ,reduced GFR are common; Less than one-half of the patients had concurrent lupus nephritis. more than one-half of whom progressed to ESKD.
- Importantly, the development of collapsing FSGS in Black patients with SLE is associated with risk polymorphisms in the *APOL1* gene.
- Collapsing FSGS has also been associated with other autoimmune conditions including adult-onset Still disease and Behçet syndrome

Collapsing FSGS not associated with HIV Etiology: Diabetic kidney disease

- Typical histopathologic and clinical features of collapsing FSGS have also been noted in patients with diabetic kidney disease (DKD).
- In a study patients with DKD, 5 percent had C-FSGS superimposed on DKD .
- Those with both lesions had more severe disease at the time of biopsy (the mean serum creatinine was 3.8 mg/dL and mean 24-hour proteinuria was 9.8 grams), and the development of ESKD was more rapid than in patients with DKD but without C-FSGS.

Collapsing FSGS not associated with HIV Clinical features

Patients with idiopathic collapsing FSGS present with a similar clinical picture as those with HIV-associated collapsing FSGS.

This can include a preceding or ongoing febrile illness, severe nephrotic syndrome, kidney function impairment at presentation, and rapid progression to ESKD.

On urinalysis, the nephrotic sediment is associated with heavy proteinuria, lipiduria, and occasionally large granular casts.

Compared with typical FSGS, collapsing FSGS presents with more severe kidney involvement, including higher levels of proteinuria (commonly over 10 g/day) and more severe kidney dysfunction.

Collapsing FSGS not associated with HIV Clinical features

- In general, kidney ultrasonography of patients with collapsing FSGS shows large echogenic kidneys (even in ESKD) as opposed to typical FSGS where smaller, shrunken kidneys are common.

- Clinical features in other secondary forms of collapsing FSGS may be more variable, including a milder phenotype (often sub-nephrotic proteinuria and less severe [AKI]) in drug-induced and ischemia-associated forms of collapsing FSGS.

Collapsing FSGS not associated with HIV pathology

- Collapsing FSGS is associated with segmental or global collapse and sclerosis of the glomerular tufts.
- Most often there is evidence of collapse and sclerosis of the entire glomerular tuft, rather than segmental collapse.
- For many pathologists the finding of collapsing features of even one glomerulus on a kidney biopsy is sufficient for the diagnosis

Collapsing FSGS not associated with HIV pathology

- Compared with classic focal FSGS, the following features on kidney biopsy are particularly suggestive of collapsing FSGS:
- Marked hypertrophy and hyperplasia of overlying glomerular epithelial cells above the collapsed areas of the tuft .
- Often severe tubular injury with cystic dilatation of the tubules filled with proteinaceous casts (proliferative microcystic transformation) and tubular degeneration.
- The wrinkling and retraction of the glomerular basement membrane

Collapsing FSGS not associated with HIV Pathology

- Histologic features that may differ between collapsing FSGS due to HIV from that due to non-HIV infection include:
- The presence of tubuloreticular structures in glomerular endothelial cells on EM with HIV-associated disease However, such structures may also be seen in collapsing FSGS associated with other conditions in which interferon signaling pathways are upregulated (eg, viral infections,SLE, and interferon therapy). Tubuloreticular lesions may be absent in patients with HIV nephropathy who have been treated with antiretroviral therapy.
- A greater incidence of proliferative microcystic transformation with HIV nephropathy

Collapsing FSGS not associated with HIV DIAGNOSIS: Establishing the diagnosis

- The diagnosis of collapsing FSGS should be suspected in any patient presenting with nephrotic syndrome, especially if acute kidney injury is also present.

- A kidney biopsy is required to establish the diagnosis and exclude other possible causes of the nephrotic syndrome

Collapsing FSGS not associated with HIV Diagnosis: Evaluation for associated conditions

- History and physical examination, including an assessment of the following:
- Exposure to drugs and/or toxins associated with collapsing FSGS (eg, bisphosphonates, anabolic steroids, interferon)
- History of infections (viruses [eg, HIV, parvovirus B19, SARS-COV-2, CMV,EBV, TB, malaria, leishmaniasis)
- History of another glomerular disease (eg,SLE, IgA nephropathy,DKD)
- (CBC) with platelet count, to assess for anemia and thrombocytopenia.
- Examination of the PBS for schistocytes.
- Tests for HIV, parvovirus B19, SARS-COV-2, cytomegalovirus, and EBV.
- ANA
- Serum ferritin concentration.
- Genetic testing for APOL1 variants

Collapsing FSGS not associated with HIV TREATMENT;General measures in all patients

- General supportive measures in all patients with collapsing FSGS include dietary sodium and protein restriction, blood pressure control, minimization of proteinuria with renin-angiotensin system inhibition, treatment of dyslipidemia, and in selected patients, anticoagulation.
- (SGLT2) inhibitors may be of benefit, but data and experience are limited.
- Other aspects of therapy include diuretics to control edema and maintenance of adequate nutrition.

Collapsing FSGS not associated with HIV TREATMENT

- **Patients with idiopathic collapsing FSGS** — There are no clinical trials to guide the optimal therapy of idiopathic collapsing FSGS.

- **Initial immunosuppressive therapy** — In general, we treat most patients with idiopathic collapsing FSGS and nephrotic-range proteinuria with immunosuppressive therapy

Collapsing FSGS not associated with HIV TREATMENT

- We suggest oral glucocorticoids as initial therapy.
- Glucocorticoids should be used with caution, if at all, in patients at high risk for infection or in patients with diabetes.
- For patients who present with large amounts of proteinuria (>10 g/day), severe hypoalbuminemia (serum albumin of <2 g/dL), **and** preserved kidney function (estimated glomerular filtration rate [eGFR] ≥45 mL/min/1.73 m^2), we prefer to add a calcineurin inhibitor (CNI; cyclosporine or tacrolimus)
- Patients with severe nephrotic syndrome (eg, proteinuria >10 g/day and serum albumin <2 g/dL) generally have a poor prognosis

Collapsing FSGS not associated with HIV Monitoring the response to therapy

- There are no specific guidelines for monitoring the response to therapy.

- In patients receiving immunosuppressive therapy, we measure routine blood chemistries, including a plasma creatinine for estimation of GFR, albumin, and urine protein-to-creatinine ratio, every two to four weeks for the first two months and, if stable, monthly thereafter.

- In patients receiving a CNI, we monitor whole blood trough concentrations on a monthly basis, aiming for cyclosporine trough levels of 125 to 225 ng/mL or tacrolimustrough levels of 5 to 10 ng/mL, although the lowest effective dose of CNI should be used to limit nephrotoxicity.

Collapsing FSGS not associated with HIV Resistant disease

- The optimal treatment for patients who do not respond to initial therapy with glucocorticoids with or without a CNI is not known.
- In patients who do not respond to initial therapy with glucocorticoids alone and who have an eGFR ≥30 mL/min/1.73 m^2, we discontinue glucocorticoids and treat with a CNI (cyclosporine or tacrolimus)
- In patients who have an eGFR <30 mL/min/1.73 m^2, we avoid using CNIs given the additional risk of nephrotoxicity in these patients. In such patients, rituximab(1 g initially followed 14 days later by another 1 g dose) is an alternative option

Collapsing FSGS not associated with HIV TREATMENT

- **Patients with associated conditions** — In general, the treatment of collapsing FSGS with associated conditions is directed at the underlying condition responsible for the collapsing FSGS. Immunosuppressive therapy is **not** typically recommended, except in a few special circumstance
- **Collapsing FSGS associated with infections** – In patients with collapsing FSGS associated with infections, treatment of the underlying infection may improve kidney outcomes
- **Collapsing FSGS associated with drugs** – In patients with collapsing FSGS associated with drugs , the primary approach to treatment is discontinuation of the offending agent

Collapsing FSGS not associated with HIV Prognosis

- In general, the prognosis of idiopathic collapsing FSGS not associated with HIV infection is poor
- One retrospective study compared kidney outcomes between 61 patients with collapsing FSGS and 126 patients with noncollapsing FSGS .At baseline, patients with collapsing FSGS had higher levels of proteinuria (12 versus 4 g/day) and lower eGFR (eGFR; 48 versus 60 mL/min/1.73 m^2).
- At a median of 69 months, patients with collapsing FSGS were more likely to have end-stage kidney disease than those with noncollapsing FSGS

Collapsing FSGS not associated with HIV Transplantation

- Kidney transplantation has been performed in patients with idiopathic collapsing FSGS.
- Recurrent disease can occur, supporting the presence of a pathogenic circulating factor, with a recurrence rate similar to that of other patterns of FSGS.
- De novo collapsing FSGS in the kidney allograft has also been described and may occur in the setting of inflammation (acute rejection or viral infections (CMV), secondary to glomerular ischemia from acute vascular occlusion (due to [TMA], atheroembolism, or cortical necrosis)

Thanks for your Attention