

Collapsing glomerulopathy: a lesion under-recognised in Pakistan

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Collapsing glomerulopathy (CG) is a distinctive but non-specific pattern of proliferative renal parenchymal injury characterised morphologically by an implosive, global and/or segmental collapse and wrinkling of the glomerular capillary walls. This is associated with a near-complete occlusion of the capillary lumen, florid hypertrophy and hyperplasia of the visceral epithelial cells (VECs), and severe tubulo-interstitial lesions.¹

A similar morphology was also reported in 1980s in a renal lesion caused by infection with human immunodeficiency virus type 1 (HIV-1), and was known as HIV-associated nephropathy (HIVAN). In fact, five of the six cases reported in the first case series of CG were HIV positive.² This led other authors to speculate that the disease may be caused by HIV-1 infection.³ However, with growing recognition and reporting, the lesion is now known to be caused by a large variety of un-related clinical conditions and aetiologic agents.⁴⁻⁷ The list of aetiological agents is expanding continuously and encompasses the whole range of injurious agents from genetic aberrations, infections, drugs and chemicals to autoimmune disorders, neoplastic conditions and ischaemic diseases.¹⁻⁷

The lesion was initially reported in native kidneys,² but with time, more and more reports have appeared in literature on the occurrence of the condition, either as recurrent or de novo form, in renal allografts.⁸⁻¹⁰ Additionally, while the majority of earlier studies on CG originated from the Western countries, especially the United States of America,^{1,2} more and more reports have emanated from centres in the developing countries in the recent past.³⁻¹⁰ These attest to the cosmopolitan distribution of the disease. More importantly, the disease is increasing in its incidence and is becoming a major cause of end-stage renal disease (ESRD) in many parts of the world.¹

The issue of the nomenclature and nosologic classification of the lesion is also not yet settled.¹ Although officially it is classified as a variant of focal segmental glomerulosclerosis (FSGS), it has more

differences than similarities with the latter lesion and many researchers feel that sooner or later it will be classified separately from FSGS.⁶

Aetio-pathogenesis

Although the aetiological and clinical associations of CG are well characterised, the exact triggering agent and the pathogenesis of the condition still remain largely unresolved. The discovery of murine models of the disease, reporting of some familial cases and the occurrence of CG in renal transplant setting have helped markedly in increasing the understanding of the aetio-pathogenetic pathways of the lesion.^{1,6}

The key question in the pathogenesis of the condition is how so many varied conditions and aetiological agents lead to the stereotyped appearance of the lesion on renal biopsies? Although largely speculative, a "best-fit" model has been suggested as the unifying final common pathway. Of course, this pathway may be triggered by a variety of aetiological agents and clinical conditions and is conditioned by the racial and genetic make-up of the individual. The two major links in this pathogenetic pathway consist of some sort of dysregulation of the

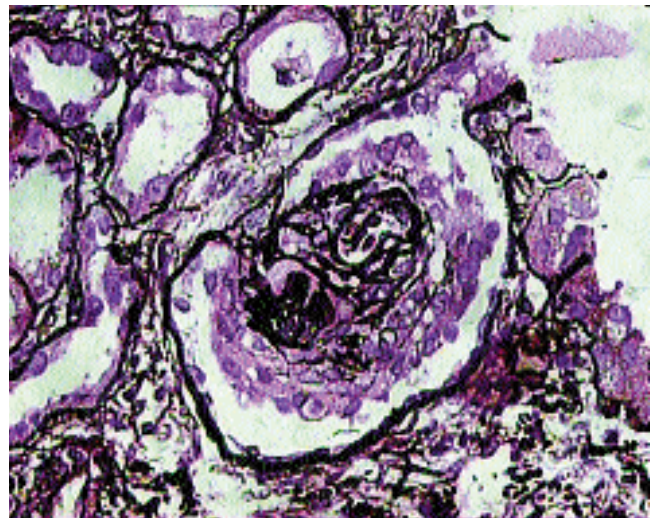


Figure: Medium-power view showing global collapse of capillary tufts associated with marked hypertrophy and hyperplasia of podocytes, forming pseudo-crescent. This is the defining lesion of collapsing glomerulopathy. Surrounding parenchyma shows moderate tubular atrophy and interstitial inflammation. (Silver stain, $\times 200$).

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immune system and the mitochondrial function.¹

Signs and Symptoms

Clinically, idiopathic CG presents with heavy proteinuria and nephrotic syndrome in the vast majority of cases. Variable degree of renal dysfunction is also commonly noted at the time of presentation. Although the disease involves mostly the adults, but reports of its occurrence in children have also emerged. One notable epidemiological feature of the disease is the preponderance of black race in the affected patient population. The disease is characterised by rapid downhill course to ESRD in a relatively short period of time. Some cases have responded to high dose steroids and other empirical therapy. Occasional cases of spontaneous remission have also been reported.⁶

The disease has an almost uniformly poor prognosis both in the native and transplanted kidneys. The vast majority of patients rapidly progress to ESRD or graft loss even with the currently available treatment. However, it must be noted that the prognosis also partly depends on the underlying cause of the lesion.¹⁻⁵

Differential

The pathology of the disease is highly characteristic and the only other lesions which may come in the differential diagnosis of the condition include the crescentic glomerulonephritis (CresGN) and the cellular variant of FSGS. The disease can easily be diagnosed on light microscopic examination of the renal biopsies. In problematic cases, immunohistochemistry may help in resolving the differential, especially with CresGN. Immunofluorescence study is also usually negative or shows nonspecific segmental deposits of IgM and complement components.⁶

Therapy

There is no specific therapy for the disease at present. The currently used regimen in non-HIV infected patients employs the same strategy as used for ncFSGS and consists of high dose steroids and other immunosuppressive agents, along with plasmapheresis in selected cases. The overall success rate of these regimens is however low. Insights from the newer molecular and genetic studies into the pathogenesis of CG may change

this uniformly poor outlook for this treatment refractory form of renal disease in both the native and the transplanted kidneys.^{1,6} One therapeutic strategy that has proved useful in preclinical testing in the animal models is the use of small molecule inhibitors of cell cycle regulatory proteins causing growth arrest of the renal epithelial cells or the use of differentiating agents such as retinoic acid derivatives to induce differentiation of the aberrantly proliferating cells. These preliminary studies suggest that rational approaches to the treatment of CG based on the knowledge of pathogenesis rather than of empiricism may soon be available.^{1,6}

In conclusion, although much progress has been made in understanding the etiology and pathogenesis of CG during the last two decades, the story has not yet been fully unfolded. The recent advancements in understanding the pathogenetic pathways are likely to open up new potential targets for research into and the development of the rational therapy of this disease in both the native and the transplanted kidneys in not too distant future.

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