

# Spectrum of HCV-Related Glomerular Disease

*Charles Alpers, MD*



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HCV has been associated with multiple extrahepatic manifestations, including cryoglobulinemia, glomerulonephritis, skin disorders (porphyria cutanea tarda, lichen planus), arthritis, a sicca-like syndrome, Mooren's corneal ulcer, and lymphoproliferative disorders (1, 2). It has been shown that in humans the principal renal manifestation of chronic hepatitis C infection is development of a membranoproliferative glomerulonephritis (MPGN) most often associated with cryoglobulinemia (3, 4). Indeed, it is now regarded that HCV infection is the pathogenetic basis for the great majority of cases of what were previously thought to be idiopathic MPGN and essential mixed cryoglobulinemia (3, 4). The renal manifestations are usually associated with long-standing (i.e. a greater than 10 year history) HCV infection. Most often there are concurrent clinical and laboratory features of chronic active hepatitis and/or cirrhosis. HCV glomerular disease has been most frequently identified in adult males; this disease process is rare in children. While the percentage of HCV infected patients with such manifestations is small, the problem is significant as the population at risk is so large.

HCV-associated glomerular disease often presents as a component of a mixed cryoglobulinemia syndrome (1-4). Patients clinically have features characteristic of cryoglobulinemia, including palpable purpura, arthralgias, neuropathy, and weakness. Rarely, the presentation may include severe vasculitis with abdominal pain, or features referable to other foci of solid organ involvement such as pulmonary, cardiac, or CNS involvement. Hepatomegaly is common. Particular renal manifestations of HCV associated glomerular disease include nephrotic or non-nephrotic proteinuria and microscopic hematuria (1). Renal insufficiency, frequently mild, is commonly identified. It is important to realize that renal manifestations may occur in the absence of other signs of cryoglobulinemia or liver disease, and that the diagnosis of hepatitis C may be made in retrospect after various components of a renal evaluation process have been completed.

Laboratory testing is particularly important in establishing the diagnosis. By definition, affected patients must demonstrate the presence of anti-HCV antibody by either enzyme immunoassay or recombinant immunoblot assay. If searched for, patients typically will demonstrate the presence of viremia (circulating HCV RNA by PCR analysis). Liver transaminases are elevated in approximately 70% of affected patients. The majority of patients show the presence of a circulating Rheumatoid factor, and typically demonstrate low levels of all components of the complement cascade. Tests for ANCA are almost always negative. Circulating cryoglobulins can be detected in approximately 50-70% of affected patients.

The commonest renal manifestation of hepatitis C infection is some form of immune complex deposition process resulting in glomerulonephritis. Using a broad definition of membranoproliferative glomerulonephritis (MPGN) as a pattern of glomerular injury, it is clear that the greatest number of affected patients will be found to have this pattern of injury when diagnostic renal biopsies are obtained.

MPGN typically presents many years after initial infection with the hepatitis C virus. As indicated above, the majority of cases reported to date, but not all have concomitant clinical features of mixed cryoglobulinemia, and the biopsy appearance of glomerular injury may reflect this noteworthy association. In the MPGN associated with cryoglobulinemia, termed cryoglobulinemic glomerulonephritis by some, there may be a marked infiltration of glomerular capillaries by leukocytes, typically with a large component of monocytes. Glomeruli show accentuated lobulation of the tuft architecture, and may show some combination of increased mesangial cellularity, mesangiolytic, capillary endothelial swelling, splitting of capillary basement membranes, and sometimes, intracapillary globular accumulations of eosinophilic material representing precipitated immune complexes/cryoglobulins. On ultrastructural examination, the visualized immune complexes, typically subendothelial in location, may have a finely fibrillar or tactoid pattern of organization, a distinctive features of some cryoglobulin deposits.

In non-cryoglobulinemic MPGN, the features are similar to that described above except the features of mesangiolytic, marked leukocyte influx and intracapillary accumulations are less likely to be apparent. Both subendothelial and subepithelial

immune complexes can be identified by electron microscopy, typically without distinctive substructure. In both forms of HCV associated MPGN, mesangial and capillary wall deposition of IgM, IgG, and C3 are frequently, but not invariably, demonstrated.

Other forms of glomerular injury have been documented as well (5). Both individual case reports and small series have reported membranous glomerulonephritis (MGN) in HCV infected patients (5, 6). The clinical features and pathology in these cases do not distinguish those patients from those with idiopathic or other secondary forms of MGN. Other forms of immune complex mediated glomerulonephritis, such as IgA nephropathy, may occur in these patients. We believe there also may be a noteworthy population of HCV-infected patients who develop glomerular injury corresponding to focal and segmental glomerulosclerosis. Many of these patients have a history of intravenous drug abuse as a probable route of infection with the hepatitis C virus. Recently, cases demonstrating an association of HCV infection and fibrillary glomerulonephritis and immunotactoid glomerulopathy have been reported (7).

Occasional patients will have small vessel vasculitis, and necrotizing inflammation of interlobular arteries and arterioles may dominate their renal biopsy picture (1).

Recurrence of MPGN in renal allografts has been suspected in a small number of patients, but the extent of this problem has not yet been adequately studied. Establishing the diagnosis of MPGN in the transplant setting is made especially difficult by the similarities of the glomerular lesions to those of transplant glomerulopathy (8-10). Patients with HCV may also be at greater risk for rejection than uninfected patients.

The precise pathogenetic sequence of injury resulting in glomerulonephritis is not known. Currently, it is thought that glomerular injury in this setting results from the deposition of circulating immune complexes which contain HCV and anti-HCV antibody and which may contain rheumatoid factors. One limitation of our understanding of pathogenetic factors is the lack of reliable reagents that might allow the identification of virus or viral peptides in tissue sections by such techniques as immunohistochemistry or in situ hybridization. Our understanding is further limited by the lack of a relevant experimental model. No animal model of Hepatitis C infection and target organ injury with similarities to human disease currently exists. Surrogate animal models of MPGN and cryoglobulinemic MPGN in particular may facilitate our understanding of downstream manifestations of disease. Approaches towards this end have included use of murine hybridomas that have produced cryoprecipitable immunoglobulins analogous to Type I cryoglobulins in humans, but infusion studies of these immunoglobulins have not resulted in production of MPGN-like lesions in animals. Another approach has been to use human cryoglobulins removed by therapeutic apheresis and reinfuse the cryoglobulins into rodents. Infusion of some of these cryoglobulins has resulted in glomerular lesions similar to those encountered in the patients from whom they were derived. While an interesting proof of principle, these models are not available for extended use in studies of pathogenesis or therapeutic interventions. Two intriguing models of spontaneous MPGN have been reported in large animals (dogs, pigs) with genetic deficiencies in the complement system. While worthy models for study, both of these systems have limited utility as a generalized animal model because of a lack of sufficient reagents to characterize disease in these species and the high expense of conducting studies in large mammalian species. Some genetic models of murine lupus (e.g., MRL/lpr and BXSB) also result in development of cryoglobulins, but this development is neither uniform nor controllable, and both the lack of predictability and complexity of immunologic abnormalities make experimental manipulation of such strains difficult to interpret except in very broad measures. Most recently several relevant mouse models of demonstrable or probable mixed cryoglobulinemia and cryoglobulinemic MPGN, almost identical to that which occurs in humans, have been identified. These models may be useful for the identification of strategies that will lead to successful treatment of this disease. There are many opportunities for such interventions - examples would be interruption of the initial process of immune complex deposition, dampening the amplification of inflammatory injury, subsequent immune complex deposition, amelioration of disease progression (e.g., events/growth factors/cytokines controlling cell proliferation, matrix deposition), or enhancement of disease resolution.

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