

Cryoglobulinemia and HCV Infection

Vincent Agnello, PhD



[Print this page](#)

The specific etiologies of the cryoglobulins in HCV infection are unknown but may relate to two specific immunologic features of HCV: the virus evades immune elimination in most patients and in some patients it induces monoclonal rheumatoid factors (RF). As a result of these features there is chronic infection associated with chronic formation of an immune complex containing polyclonal, oligoclonal and monoclonal immunoglobulins. Some immune complexes precipitate in the cold *in vitro*, i.e., cryoglobulins. Only some immune complexes are associated with disease. The clinical syndrome of mixed cryoglobulinemia (Meltzer-Franklin syndrome) is a systemic vasculitis that affects mainly skin, kidneys, and nerves. In type II, the cryoglobulins consist of polyclonal IgG and monoclonal IgM RF; in type III, both the IgG and IgM RF are polyclonal. Approximately 90% patients with the mixed cryoglobulinemia syndrome are HCV infected. A highly restricted monoclonal RF that bears an antibody-combining site epitope called the WA cross-idiotype is present in approximately 80 % of patients with symptomatic type II cryoglobulinemia. HCV along with VLDL appear to be selectively concentrated with type II cryoglobulins *in vitro*.

Clinical manifestations occur predominantly with type II cryoglobulins. There appears to be a variable pathogenic role of HCV in mixed cryoglobulinemia. The palpable purpura (leukocytoclastic vasculitis) lesions of the skin appear to be due to complexes of HCV, mRF and RF formed *in situ*. In contrast, HCV has not been detected in the glomerular deposits in the membrano-proliferative glomerulonephritis (MPGN) or in the vascular deposits in the peripheral nerve lesions. Reports of HCV antigen in glomerular deposits in MPGN are problematic because the antibody probes for antigens that were used were not F(ab')₂ preparations and could react with RF in the deposits.

The surprising detection of HCV in palpable purpura lesions led to the discovery that HCV and other members of the Flaviviridae family undergo endocytosis via the LDL receptor. This mechanism can result in entry of HCV into cells permissive and non-permissive to HCV replication that have high concentration of LDL receptor. This mechanism appears to be responsible for the presence of HCV in the proximal tubule epithelial cells in MPGN.

There is no standardized therapy for mixed cryoglobulinemia secondary to HCV infection. The current regimens for HCV infection require modification for patients with mixed cryoglobulinemia because of the high relapse prevalence. The cryoglobulins in many cases appear to persist at low levels after HCV is no longer detectable in the serum. Protocols that use end of therapy criteria (ECT) designed specifically for patients with cryoglobulinemia are needed. ECT that should be tested in addition to undetectable serum HCV and cryoglobulins are clearance of monoclonal RF producing cells from the blood that are detected by B cell clonal expansion analysis, and clearance of HCV and lymphoid aggregates in the liver.

References

1. Agnello V. Mixed cryoglobulinemia and other extrahepatic manifestations of HCV infection. In: Hepatitis C. Eds, T.J. Liang, J.H. Hoofnagle, Academic Press, 2000, pages 295-313.
2. Agnello, V Mixed cryoglobulinemia after hepatitis C virus: more or less ambiguity. *Ann Rheum Dis* 57: 701-3, 1998.
3. Pucillo L.D. and Agnello V. Membranoproliferative glomerulonephritis associated with hepatitis B and C viral infections from virus-like particles in the cryoprecipitate to viral localization in paramesangial deposits, problematic investigations prone to artifacts. *Curr Opin in Nephrol Hypertension* 1994; 3:463-70.
4. Agnello V Therapy for cryoglobulinemia secondary to hepatitis C virus: the need for tailored protocols and multi-clinic studies. *J. Rheum.* 2000;27 :2065- 7.