Hepatitis C: A Multifaceted Disease
Review of Extrahepatic Manifestations
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Purpose: To review the available data on the association between hepatitis C virus (HCV) infection and conditions reportedly related to infection with the virus and to assess the clinical implications of these associations.

Data Sources: Pertinent articles were identified using the Paperchase database, which simultaneously searches the MEDLINE (1966 to present), Health (1975 to present), AIDSLINE (1980 to present), and Cancerlit databases.

Study Selection: All studies for a given association were reviewed, but special attention was paid to randomized controlled trials where applicable.

Results: According to the available data, HCV infection appears to be strongly associated with essential mixed cryoglobulinemia, membranoproliferative glomerulonephritis, and porphyria cutanea tarda. Evidence strongly suggests that HCV has a direct pathogenetic role in some patients with the first two conditions. The association with Mooren corneal ulcers and autoimmune thyroiditis is suggested, but more data are needed to confirm it. The data for the association between HCV infection and the Sjögren syndrome, lichen planus, and idiopathic pulmonary fibrosis remain weak. Although interferon therapy has been effective in patients with both essential mixed cryoglobulinemia and membranoproliferative glomerulonephritis, a high relapse rate has been noted in the latter condition.

Conclusions: Patients with essential mixed cryoglobulinemia, membranoproliferative glomerulonephritis, and porphyria cutanea tarda should be tested for HCV infection. Conversely, signs and symptoms of these conditions should be sought in patients with chronic HCV infection. Interferon therapy is currently recommended only for patients with symptomatic essential mixed cryoglobulinemia.

The major cause of transfusion-associated non-A, non-B hepatitis was identified in 1989 to be an RNA virus, which was named hepatitis C virus (HCV) (1). With the availability of more reliable assays, HCV infection is emerging as an extremely common and insidiously progressive disease that may result in chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. According to the National Health and Nutrition Examination Survey (a serosurvey), the prevalence of antibodies to HCV in the general U.S. population is 1.4%, which corresponds to 3.5 million persons (2). Whereas 2% to 5% of adult patients with acute hepatitis B infection develop chronic hepatitis B, an estimated 50% to 75% of patients with acute hepatitis C develop chronic infection. Moreover, chronic HCV infection rarely, if ever, spontaneously resolves. Because the virus was discovered so recently, many aspects of this disease, including clinical manifestations, natural history, and treatment, are incompletely understood.

Chronic HCV infection has been associated with several extrahepatic conditions, including essential mixed cryoglobulinemia, porphyria cutanea tarda, membranoproliferative glomerulonephritis, autoimmune thyroiditis, and the Sjögren syndrome. We review the available data on these conditions and assess their clinical implications and therapeutic options.

Methods

We identified pertinent articles using the Paperchase database, which simultaneously searches the MEDLINE (1966 to present), Health (1975 to present), AIDSLINE (1980 to present), and Cancerlit databases. We reviewed all studies for a given association but paid special attention to randomized controlled trials where applicable.

Essential Mixed Cryoglobulinemia

Several recent studies have established a strong link between HCV infection and essential mixed cryoglobulinemia, a multisystem disorder of unknown cause. This condition is characterized by deposition of circulating immune complexes in small and medium-sized blood vessels and results in arthralgias, the Raynaud syndrome, and purpura. Systemic vasculitis, peripheral neuropathy, and glomerulonephritis are also occasionally seen. Many patients have the clinical triad of purpura, weakness, and arthralgias. The diagnosis is based on the presence of unique immunoglobulins (IgG, IgM, or both). The name cryoglobulin stems from the tendency of these immunoglobulins to precipitate at cold temperatures.

Cryoglobulinemia has been categorized according to the clonal composition of immunoglobulins into type I (monoclonal only), type II (mixed monoclonal and poly-
Table 1. Prevalence of Hepatitis C Virus in Serum Samples of Patients with Essential Mixed Cryoglobulinemia*  

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients n</th>
<th>Prevalence %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferri et al. (5)</td>
<td>26</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>Agnello et al. (6)</td>
<td>19</td>
<td>42</td>
<td>84</td>
</tr>
<tr>
<td>Misiani et al. (7)</td>
<td>51</td>
<td>66</td>
<td>81</td>
</tr>
</tbody>
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* HCV = hepatitis C virus; RIBA = recombinant immunoblot assay.

clonal), and type III (polyclonal only). Although type I cryoglobulinemia is usually associated with lymphoproliferative disorders, type II and III (the mixed cryoglobulinemia) may or may not be associated with this or other disorders such as autoimmune diseases, chronic liver disease, or viral infections such as Epstein-Barr virus infection. Because of the high prevalence of coexisting essential mixed cryoglobulinemia and hepatocellular abnormalities, it was postulated that hepatotoxic viruses may be involved in the pathogenesis of this disease. Hepatitis B virus was first studied in this regard, but no definitive etiologic role could be shown (3).

Table 1 summarizes the results of three studies that examined the prevalence of HCV in patients with cryoglobulinemia by testing for HCV antibody with recombinant immunoblot assay (RIBA) and for HCV RNA with polymerase chain reaction. The association is striking. Ferri and colleagues (4) were one of several groups that detected, in an uncontrolled preliminary study, a high prevalence of HCV RNA in patients with essential mixed cryoglobulinemia. In a more recent study, Ferri and colleagues (5) noted that 96% of 26 patients with essential mixed cryoglobulinemia were positive for HCV antibody and that 91% were positive for HCV RNA.

Agnello and colleagues (6) found a high frequency of HCV antibody and HCV RNA in the serum of patients with essential mixed cryoglobulinemia and that both HCV antibody and RNA were concentrated to approximately 10-fold and 1000-fold, respectively, in the type II cryoprecipitates. Serum samples from nine patients with type I cryoglobulinemia, used as controls, were negative for HCV antibody and HCV RNA. However, HCV antibody or HCV RNA was present in the serum of 5 of 10 patients with type III cryoglobulinemia.

Misiani and associates (7) also showed a high prevalence of HCV antibody (66%) and HCV RNA (81%) in the serum of patients with cryoglobulinemia associated with glomerulonephritis. According to both enzyme-linked immunosorbent assay (ELISA) and RIBA, 94% of patients had HCV antibodies in the cryoprecipitates. Only 2% of the controls—patients with noncryoglobulinemic glomerulopathies—had HCV antibodies by ELISA.

Lunel and coworkers (8) prospectively followed 226 patients with chronic liver disease; 127 had hepatitis C infection, 40 had hepatitis B infection, and 59 had chronic liver disease caused by other factors. Controls were 136 healthy blood donors. Cryoglobulinemia was discovered in 54% of patients with hepatitis C, 15% of those with hepatitis B, 32% of those with other chronic liver diseases, and 4% of controls. About one third of the patients with hepatitis C and cryoglobulinemia had type II cryoglobulinemia, and two thirds had type III. Twenty-one percent of these patients had clinical symptoms compatible with cryoglobulinemia, with approximately equal percentages of type II and type III. In agreement with the findings of Agnello and colleagues (6), Lunel and coworkers found that HCV RNA and proteins were concentrated in the cryoprecipitates. Another recent prospective study showed that 36% of 59 consecutive patients with HCV RNA in their serum had cryoglobulinemia; however, the type was not specified (9).

A pathogenetic role of HCV in the vasculitis of patients with essential mixed cryoglobulinemia was shown in an Italian study (10) in which the investigators searched for the presence of HCV-associated antigens in skin and liver biopsy specimens of five groups of patients. Group 1 consisted of 15 patients with type II essential mixed cryoglobulinemia who were positive for both HCV antibody and HCV RNA. Group 2 consisted of 7 patients without essential mixed cryoglobulinemia who were also positive for HCV antibody and HCV RNA and had chronic active liver disease. The remaining three groups of patients were negative for HCV antibody and HCV RNA and had type II essential mixed cryoglobulinemia (group 3), noncryoglobulinemic vasculitis (group 4), or lichen ruber planus (group 5). Only patients in group 1 (40%) had immunohistochemical evidence of HCV-associated antigens in their skin biopsy specimens. These antigens were seen in the liver biopsy specimens of 64% of patients in group 1 and 71% of patients in group 2. No HCV-associated antigens were seen in the liver or skin biopsy specimens of the patients negative for HCV antibody and HCV RNA.

The idea that HCV may be an important etiologic agent of essential mixed cryoglobulinemia is also supported by the fact that antiviral therapy with interferon-α is effective in treating this associated condition. Misiani and colleagues (11) reported results of a randomized controlled trial in which 27 of 53 patients with HCV and type II cryoglobulinemia received interferon and the remaining 26 did not. Sixty percent of the treatment group had no detectable HCV RNA at the end of treatment and had significant improvement in cutaneous vasculitis, IgM, and cryoglobulins compared with controls. Relapse of viremia after therapy was discontinued resulted in worsened cryoglobulinemia. In another randomized controlled crossover trial (5), all 20 patients who received interferon had significantly improved purpura and serum cryoglobulin levels; a rebound phenomenon of clinical and serologic
variables was also noted after interferon therapy was discontinued.

Taken together, these studies suggest a strong causal role of HCV in the development of essential mixed cryoglobulinemia. We recommend that patients with essential mixed cryoglobulinemia be tested for HCV and, conversely, that symptoms of essential mixed cryoglobulinemia (such as arthralgias, the Raynaud syndrome, and purpura) be sought in patients with a diagnosis of chronic HCV infection. Serum cryoglobulin levels should be measured if such symptoms are present. Treatment with interferon-α should be instituted in patients with symptomatic cryoglobulinemia associated with HCV infection.

Porphyria Cutanea Tarda

Porphyria cutanea tarda, the most common form of porphyria, is caused by reduced activity of uroporphyrinogen decarboxylase. In the sporadic form of the disease, type I, the enzyme activity is decreased to 50% in the hepatocytes only, whereas in the less common familial form, type II, the enzymatic defect is also present in other cell types, such as erythrocytes (12). This enzymatic defect is essential but not sufficient for the clinical manifestations of porphyria cutanea tarda. The extrinsic factors that modulate this expression include alcohol consumption, estrogens, and iron overload. The onset of porphyria cutanea tarda is characterized by the development of cutaneous lesions, increased skin fragility, bruising, and the appearance of vesicles and bullae that may become hemorrhagic (13). Pigmentation, depigmentation, hirsutism, and sclerodermoid appearance can develop over time.

Hepatic dysfunction is seen in almost all cases of porphyria cutanea tarda, the cause of which is unknown. The histologic changes vary and include chronic persistent or chronic active hepatitis, cirrhosis, and moderate siderosis. This observation and the availability of reliable assays for HCV led three groups of researchers to almost simultaneously seek an association between porphyria cutanea tarda and HCV infection (14–16). All three groups found a strong association. Antibody to HCV was found in 62% of 34 patients (14), 82% of 74 patients (15), and 79% of 100 patients (16). Hepatitis C virus RNA was confirmed in 66% of patients in one study (15) and in 100% of patients positive for the antibody to HCV in the other study (16). The prevalence of HCV antibody was significantly higher in patients with porphyria cutanea tarda than in healthy blood donors and controls with nonhepatic diseases \( P < 0.001 \) (15). Hirera and colleagues (16) reported that 79% of patients with sporadic porphyria cutanea tarda and none of the patients with familial porphyria cutanea tarda were positive for HCV by the RIBA II assay. These investigators also noted that the prevalence of HCV increased with the severity of histologic liver damage, ranging from 20% in patients with noninflammatory changes to 100% in patients with cirrhosis.

Navas and colleagues (17) retrospectively studied 34 patients with the sporadic form of porphyria cutanea tarda for the presence of HCV RNA in the liver, peripheral blood mononuclear cells, and serum. Hepatitis C virus RNA was present in the liver and peripheral blood mononuclear cells of all patients but in the serum of only 45% of patients. This observation suggests that the presence of HCV RNA in patients with porphyria cutanea tarda and any other patients may be underestimated when only the serum is tested. Only two of these patients were positive for the hepatitis B surface antigen, both of whom had coinfection with HCV.

In the study by Herrero and associates (16), many (66%) patients tested at the time of diagnosis of porphyria cutanea tarda were positive for HCV; this finding suggests that the viral infection may act as a trigger for porphyria cutanea tarda in predisposed persons. The mechanism of this trigger remains largely speculative. A decrease in the intracellular glutathione concentration induced by HCV infection has been postulated as one of the factors. Other researchers have suggested that HCV decompartmentalizes iron to create "free iron," a process that may lead to the formation of active free radicals and oxidation of uroporphyrinogens (18). Patients with porphyria cutanea tarda should be tested for HCV. Treatment of porphyria cutanea tarda has traditionally included phlebotomy and chloroquine. However, no data are available on interferon treatment in patients with porphyria cutanea tarda and chronic hepatitis C.

Membranoproliferative Glomerulonephritis

Several studies have indicated that hepatitis B infection causes both membranous and membranoproliferative glomerulonephritis by showing viral antigens in the glomerular immune deposits. Recent studies by Johnson and associates (19, 20) and others (21–25) suggest that this immunologic renal disease may also be mediated by HCV infection. Johnson and associates (19) described the clinical, pathologic, and immunologic features of eight patients with confirmed HCV infection and proteinuria. Examination of renal biopsy specimens from all eight patients showed membranoproliferative glomerulonephritis characterized by the deposition of IgG, IgM, and C3 in cryoglobulin-like structures. Cryoprecipitates from the three tested patients contained HCV RNA and HCV antibodies. In this study (19), hepatitis C virus RNA and antibodies could not be localized to glomerular lesions. However, Yamabe and colleagues from Hirosaki, Japan, have localized the c22 antigen of HCV to the glomerular lesions in patients with membranoproliferative glomerulonephritis (Yamabe H. Unpublished data; personal communication). Another group (26) claims to have found HCV-like particles in the mesangium of a patient with HCV-related hepatitis and diffuse proliferative glomerulonephritis. Corroboration of these results by other investigators would strongly support a direct role of HCV in the cause of membranoproliferative glomerulonephritis.

The results of interferon treatment of membranoproliferative glomerulonephritis have been disappointing. Johnson and colleagues (20) reported their results on a series of 14 patients who had received a standard interferon dose of 3 MU three times per week for at least 6 months. Although treatment was associated with significantly decreased (65%; \( P < 0.005 \)) proteinuria and improved liver function test results, renal function did not change. Patients in whom HCV RNA in the serum disappeared had a better clinical response. However, viremia and renal disease relapsed in all patients after cessation of therapy.
Yamabe and coworkers (27) described a patient with HCV infection, cryoglobulinemia, the nephrotic syndrome, and membranoproliferative glomerulonephritis who received subcutaneous interferon, 10 MU/d for 2 weeks, followed by 10 MU three times per week for 6 additional weeks. Within 4 weeks of starting therapy, proteinuria had dramatically improved and HCV RNA in the serum had disappeared. At 1 year of follow-up, the patient was in complete clinical remission, serum samples tested negative for HCV RNA, and histologic improvement was noted on renal biopsy specimens. This outcome suggests that different protocols using higher doses of interferon or a more prolonged course of treatment need to be studied.

A controlled study by Misiani and colleagues (7) further supports the idea of HCV-mediated glomerulonephritis; these investigators found a high prevalence of HCV antibody (66%) and HCV RNA (81%) in the serum of patients with cryoglobulinemia-associated glomerulonephritis. Only 2% of the controls (patients with noncryoglobulinemic glomerulopathies) had HCV antibodies. These results are similar to those reported by Yamabe and colleagues (23), who found a 60% prevalence of HCV in a random sample of 10 patients with membranoproliferative glomerulonephritis. Many important questions, such as the nature of the inciting antigens, the composition of circulating and deposited immune complexes, host predisposition, and the degree to which certain HCV genotypes predominate, need further investigation. An important implication of the above findings is that instead of the broad-based immunosuppression traditionally used for most forms of immune-complex glomerulonephritis, more specific therapies for this disease could be used as more effective antiviral agents become available.

The Sjögren Syndrome

Given the strong association between HCV infection and essential mixed cryoglobulinemia and the high prevalence of idiopathic Sjögren syndrome in essential mixed cryoglobulinemia (approximately 15% [28]), an association between HCV infection and the Sjögren syndrome has been postulated. Haddad and coworkers (29) found lymphocytic sialadenitis, resembling that seen in the Sjögren syndrome, in 16 of 28 patients (57%) with HCV infection and in only 1 of 20 controls (5%). Only 10 of these 28 patients had xerostomia, and none had xerophthalmia. The prevalence of cryoglobulinemia in these patients is unknown. More recently, researchers of a larger study (30) found a 14% prevalence of pathologic abnormalities resembling the Sjögren syndrome in patients with HCV infection compared with 0% in controls without HCV infection (30). Thirty-six percent of these patients with HCV infection had cryoglobulinemia. Other researchers (31, 32), however, did not find such an association. King and colleagues (33) found that all 48 of their patients with SS-A and SS-B autoantibodies, characteristic of the Sjögren syndrome, and no cryoglobulinemia were negative for HCV antibody or HCV RNA. Confirmation of an association between HCV infection and the Sjögren syndrome would suggest, albeit indirectly, that cryoglobulinemia may have a role in this association.

Miscellaneous Conditions

Other conditions, generally of autoimmune cause, have been reported to be associated with HCV, but these observations have not been well studied. These conditions include autoimmune thyroiditis, lichen planus, Mooren corneal ulcers, and idiopathic pulmonary fibrosis. In a prospective controlled study of 72 patients with chronic HCV infection, 9 had thyroid autoantibodies before interferon treatment (34). Nested polymerase chain reaction was used to confirm active viremia in all these patients. Because all patients with autoantibodies were women, the investigators recommend checking thyroid functions in women with chronic HCV infection.

Lichen planus has been known to be associated with chronic liver disease. The prevalence of liver disease in patients with lichen planus has been reported to be as high as 35% (30). A large multicenter Italian study (35) has determined that the relative risk for lichen planus in patients with various liver conditions ranges from 1.6 (patients with liver disease requiring hospitalization or specialist consultation) to 5.5 (patients from whom liver biopsy specimens were obtained). The nature of liver injury in lichen planus has been unclear. Several small reports have recently implicated HCV as a possible candidate (30, 36–38). Although lichen planus disappeared in one patient after interferon therapy was given (39), a substantial exacerbation has also been reported in another patient (40). Therefore, until more data are available, caution is warranted before interferon is used in patients with chronic HCV infection and lichen planus.

Conflicting reports have appeared regarding the prevalence of HCV infection in patients with idiopathic pulmonary fibrosis. Although Japanese researchers showed a higher prevalence of HCV in such patients compared with the general population (41), other investigators could not reproduce these findings (42). Wilson and colleagues (43) described two patients with Mooren corneal ulcers who were found to be HCV positive by nested polymerase chain reaction and whose ulcers responded to interferon treatment. Mooren corneal ulcer is a chronic and painful disorder that involves the circumference of the peripheral cornea and may progress to loss of vision. Although occasional cases are associated with eye surgery, trauma, or herpes zoster, most cases are idiopathic. Immunosuppression can be beneficial, but many cases are refractory to all forms of treatment. The ulcers in the two patients described by Wilson and colleagues did not respond to immunosuppressive therapy but did respond interferon-a2b. The ulcers worsened in one patient when he stopped receiving interferon treatment and improved again after therapy was reinstated. These interesting observations should be further confirmed.

Genomic sequence data on HCV isolates have shown that HCV exists as multiple, distinct genotypes that have been designated by Arabic numerals in the order of discovery (for example, types 1, 2, and 3). These genotypes have been further subtyped (for example, 1a, 1b, and so forth). Although many genotypes are widely distributed in the world, their distributions differ. Emerging data suggest that genotype influences both the severity of the liver disease and response to treatment with interferon. For
example, HCV type 1b seems to be more virulent, and patients infected with it respond less well to interferon than patients infected with types 2a or 2b (44). In a recent study, Pawlotsky and colleagues (9) addressed the extent to which immunologic extrahepatic manifestations of HCV infection were related to genotype-specific sequences. They sequenced 59 consecutive patients with chronic HCV into types 1, 2, and 3. Immunologic abnormalities including cryoglobulinemia, rheumatoid factor, and numerous antitissue antibodies, were seen in patients infected with any of the three serotypes; the prevalence of these abnormalities did not differ significantly among the three serotypes. Of note, the overall prevalence of these abnormalities was high. Cryoglobulinemia was seen in 36% of patients, rheumatoid factor in 71%, and at least one antitissue antibody in 41%.

Conclusion

Several investigators have suggested that HCV infection is associated with various clinical conditions (Table 2). These conditions include essential mixed cryoglobulinemia, porphyria cutanea tarda, membranous glomerulonephritis, Mooren corneal ulcer, autoimmune thyroiditis, the Sjögren syndrome, lichen planus, and idiopathic pulmonary fibrosis. According to the data, the association with essential mixed cryoglobulinemia, porphyria cutanea tarda, and membranoproliferative glomerulonephritis appears strong, and sufficient evidence suggests that hepatitis C virus is an important etiologic agent for some patients with these conditions. It is therefore recommended that patients with any of these conditions be tested for hepatitis C and, conversely, that signs and symptoms of these conditions be sought in patients with known chronic hepatitis C infection.

The association with Mooren corneal ulcers and autoimmune thyroiditis is intriguing and needs further confirmation. The data for an association with the Sjögren syndrome, lichen planus, and interstitial pulmonary fibrosis are still weak. The expression of cryoglobulinemia, rheumatoid factor, or other antitissue antibodies in patients with chronic HCV infection does not appear to be genotype-specific. Interferon treatment can currently be recommended only for patients with chronic hepatitis C and symptomatic essential mixed cryoglobulinemia. Although interferon has shown some promise for treating membranoproliferative glomerulonephritis and Mooren corneal ulcers, more data are needed before this therapy can be generally recommended. No data are available on the efficacy of interferon in treating patients with porphyria cutanea tarda and chronic hepatitis C.

Table 2. Strength of Various Associations with Chronic Hepatitis C Virus Infection and the Role of Interferon Treatment

<table>
<thead>
<tr>
<th>Association</th>
<th>Interferon Treatment</th>
</tr>
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<tbody>
<tr>
<td>Strong association</td>
<td></td>
</tr>
<tr>
<td>Essential mixed cryoglobulinemia</td>
<td>Recommended</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>No data</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>Good response but high relapse rates</td>
</tr>
<tr>
<td>Suggested association</td>
<td></td>
</tr>
<tr>
<td>Mooren corneal ulcers</td>
<td>Encouraging preliminary results</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>No data</td>
</tr>
<tr>
<td>Weak association</td>
<td></td>
</tr>
<tr>
<td>The Sjögren syndrome</td>
<td>No data; caution warranted</td>
</tr>
<tr>
<td>Lichen planus</td>
<td></td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>No data</td>
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</table>

References

21. Deouvreault JM, Alder M, Willsen M, Durez P, Yap SH. Hepatitis C
29. Haddad J, Deny P, Munz-Gothel C, Ambrosini J, Trinchet JC, Pa-
30. Pawlotsky JM, Ben Yahia M, Andre C, Voison MC, Intraor L, Rou-