

a series of articles
written by medical
professionals about
the management
and treatment of
hepatitis C

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Extrahepatic Manifestations of Chronic Hepatitis C

Although most patients with chronic hepatitis C are asymptomatic, an appreciable number will experience symptoms that are due to the liver disease and/or extrahepatic manifestations of HCV infection. Recognition of these symptoms will lead to early diagnosis and treatment of hepatitis C. Fatigue is the most common symptom of chronic hepatitis C and is most often mild. Intermittent right upper quadrant pain, anorexia and nausea occur less commonly.

Chronic hepatitis C infection predisposes patients to the development of diseases involving other organ systems including the kidneys, the skin, eyes, joints, immune system, and the nervous system. There are many extrahepatic manifestations of hepatitis C: some are relatively common (e.g., cryoglobulinemia), whereas others are infrequent and their association with hepatitis C has not been clearly defined. Only the common extrahepatic manifestations with clear association with hepatitis C will be discussed in this review.

CRYOGLOBULINEMIA

Cryoglobulins are antibody complexes that precipitate as serum is cooled and that dissolve on rewarming (1). These complexes contain hepatitis C virus (HCV) particles and can precipitate in the walls of small and medium

sized vessels. There are three types (I, II, III) of cryoglobulinemia. Type II or "mixed" cryoglobulinemia (MC) is the one most commonly associated with chronic hepatitis C infection. This type is called "mixed" because the antibodies that are found are of two kinds. One antibody is a polyclonal (i.e., from more than one group of cells) antibody (IgG), and the other antibody is a monoclonal (IgM) directed against the IgG. The frequency with which cryoglobulins are detectable in serum of patients with CHC depends on how carefully samples are handled and upon the methods used for detection of cryoglobulins. Because these proteins precipitate from serum as it is cooled, the blood must be kept at body temperature after it has been obtained until it has clotted and the serum has been drawn off. Then the serum is tested for the abnormal proteins. If this precaution is not observed, the test may be spuriously negative.

The skin, kidney, nerves and joints can be affected by cryoglobulins. Cutaneous leukocytoclastic vasculitis is a skin lesion that appears as palpable purpura (hemorrhages in the skin that result in the appearance of purplish spots or patches) that usually affects the lower extremities over the shins (Fig 1). These lesions are caused by plugging of the dermal capillaries (very small blood vessels in the skin). Successful treatment of the hepatitis

C infection with interferon (+ ribavirin) usually results in resolution of the skin lesions.



Fig 1. Leukocytoclastic Vasculitis
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Cryoglobulins also affect the nervous system in some HCV infected patients. The most frequent symptoms and signs are those of chronic sensory polyneuropathy, although acute or subacute encephalopathy has been reported as well (2,3). "Restless leg syndrome" and Guillain-Barré syndrome have also been reported (4). The mechanism of nerve involvement is thought to be MC-well-established related vasculitis of the small blood vessels that supply the nerves. There is no well-established treatment. Treatment with interferon, corticosteroids, or cyclophosphamide (cytoxan) has not shown any consistent results although some patients appear to respond to one or a combination of these drugs (5).

KIDNEY MANIFESTATIONS

The kidneys are also affected in some patients with hepatitis C. The most common kidney disease

related to hepatitis C infection is membranoproliferative glomerulonephritis (MPGN) (6). The prevalence of MPGN varies with geographical location. It is more common in Japan and is less frequently seen in France. Patients with MPGN usually complain of weakness, edema and have systemic arterial hypertension. Urine of such patients contains a lot of protein (>3.5 g/day), a condition called nephritic syndrome. Other abnormalities include low serum albumin (due to losses in the urine), decreased complement levels, and the presence of rheumatoid factor and cryoglobulins. MPGN may sometimes occur in the absence of cryoglobulinemia. Another kidney disease called membranous nephropathy (MN) is less common in HCV infected patients and is not associated with cryoglobulinemia or rheumatoid factor but is associated with heavy proteinuria (7). The mechanism of the disease is still unclear, but some studies suggest that it is caused by circulating complexes of antibodies and HCV particles directly causing damage to the kidneys as they are deposited in the glomerulus and tubules of the kidneys. Some authors recommend treatment of patients with HCV-related kidney disease even in the absence of active liver disease. The current treatment of choice for HCV infection is interferon and ribavirin. However, in patients with severe renal failure, only interferon monotherapy is recommended because ribavirin cannot be removed by dialysis. Thus, it accumulates and causes severe breakdown of red blood cells (hemolysis) and anemia.

SKIN LESIONS

Porphyria cutanea tarda (PCT) is the most common form of the porphyrias, a group of diseases characterized by defects in one or more of the enzymes involved in the production of heme. This results in the overproduction of

porphyrins or its precursors. Patients with PCT often present with blisters and vesicles on the dorsal aspects of the hands, forearms, back of the neck and face. These lesions develop in areas that are exposed to the sun and that sustain minor trauma. Increased facial hair and pigmentation changes are also noted. In some patients, as the injury becomes chronic, scarring, alopecia and thickening of the skin may occur. The skin lesions may be further complicated by deposition of calcium and formation of non-healing ulcers. See Figure 2. Patients with PCT who are of northern European origin were also found to have increased prevalence of HFE gene mutation, the gene found to be responsible in most cases of hereditary hemochromatosis. In addition to iron, heavy alcohol use and use of estrogens are also major risk factors for the development of PCT. The treatment of PCT involves dietary restriction of foods rich in iron, and avoidance of alcohol and estrogen use. Phlebotomy to remove iron is the first treatment for most patients with PCT. In patients with PCT, we recommend iron depletion by phlebotomy before initiating antiviral therapy with interferon and ribavirin. Antimalarial drugs like chloroquine have been used in the treatment of PCT as well (8).

In a large case-control study of 34,204 veterans, lichen planus, vitiligo and PCT are the skin disorders that have been found to have significant association with HCV infection (9). Lichen planus is a disease of the skin and mucous membranes that appears as violaceous, scaling papules usually located on the limbs and white reticular lesions on the mucous membranes (See Fig 3). It is suggested that this is an autoimmune response to an antigen shared by HCV particles and the basal cell layer of the skin. Vitiligo is an acquired loss of pigmentation of the skin. The loss of pigmentation is

usually found around body orifices like the mouth, eyes and nose and on the extensor surfaces of the elbows and knees as well as the wrists. Interferon has not been found to be uniformly effective in the treatment of lichen planus.



Fig 2a and 2b. Porphyria Cutanea Tarda - Reproduced with permission from Current Medicine Inc 2003



Fig 3. Lichen Planus - Reproduced with permission from Current Medicine Inc 2003

RHEUMATOLOGIC and AUTOIMMUNE MANIFESTATIONS

Myalgia (muscle pains), fatigue and arthralgias (joint pains) are common manifestations of HCV infection. HCV-related arthritis commonly presents as symmetrical inflammatory arthritis involving small joints. The joints involved in HCV-related arthritis are similar to rheumatoid arthritis (RA). This sometimes makes it difficult to differentiate true RA from HCV patients with positive rheumatoid factor but without RA. HCV-related arthritis is usually non-deforming and there are no bony erosions in

the joints. A marker called anti-keratin antibodies has been studied to differentiate true RA from HCV related arthritis. In a recent study, 71 patients who were rheumatoid factor positive were tested for anti-keratin antibodies. Anti-keratin antibodies were detected in 20/33 (60.6%) patients with true RA and only 2/25 (8%) patients with HCV-related arthritis (10). Patients with HCV-related arthritis seldom respond to anti-inflammatory medications, and although there are no controlled trials to address this issue, it has been recommended to treat these patients with combination antiviral therapy of interferon and ribavirin (11). Sjogren's syndrome (SS), an autoimmune disease characterized by dry eyes and dry mouth has been found in some studies to be more common in HCV infected patients. They differ from primary SS in that they do not have lung and kidney involvement. Thus it is recommended to test for HCV infection in patients with SS or primary SS. A study by El-Serag of 34,000 veterans failed to show a significant association between HCV infection and diabetes, SS, or autoimmune thyroid disease (9).

Interferon therapy of HCV infection may also trigger the development of autoimmune diseases, the most frequent of which is autoimmune thyroiditis (Hashimoto's thyroiditis). This may lead transiently to hyperthyroidism, but eventually to hypothyroidism (underactive thyroid) and to the need for life-long thyroid replacement therapy (Bonkovsky & Mehta).

LYMPHOMA

B-cell non-Hodgkin's lymphoma (NHL) has been linked to HCV infection. This is probably due to the long-standing stimulation of B cells caused by chronic HCV infection, although other factors must be important because most patients with CHC do not develop such lymphomas. A high prevalence of HCV was found in patients with

immunocytomas, a low-grade type of lymphoma, which was associated with cryoglobulinemia. Another study linked HCV infection and splenic B-cell lymphomas. Seven of nine patients with splenic lymphoma were treated with interferon monotherapy. Two patients who had detectable HCV RNA after treatment received combination therapy of interferon and ribavirin. All nine patients had sustained virological responses and had remission of their lymphoma, as well. On the other hand, six control patients with splenic lymphoma without HCV infection did not respond to interferon treatment at all (12). It is therefore reasonable to screen for HCV infection in patients with splenic lymphoma as well as other low grade NHL.

EYE MANIFESTATIONS

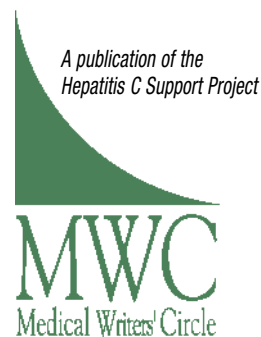
HCV infection has been associated with several eye disorders. Keratoconjunctivitis sicca (dry eyes) is part of SS. Mooren's ulcer is a rapidly progressive, painful ulceration of the cornea. The diagnosis is made by exclusion of other causes of corneal ulcer. A few cases of Mooren's ulcer and HCV infection have been reported. In at least two of these patients, the ulcers did not respond to steroid and cyclosporine drops but did respond to interferon alfa-2b (13). Damage to the retina of the eye (retinopathy, which includes cotton-wool spot formation, hemorrhages and arteriolar occlusion) is a frequent complication of interferon therapy. Fortunately, the retinopathy is usually reversible once treatment is stopped and sometimes even improves despite continuation of therapy. However, patients receiving interferon who experience visual symptoms should hold treatment and undergo careful eye examinations by eye specialists.

SUMMARY

In summary, extrahepatic manifestations of chronic hepatitis C are varied and involve a number of organ systems. Physicians and patients should be aware of these signs and symptoms, and testing for HCV should be done in patients who manifest these. This may lead to early diagnosis and successful treatment of chronic hepatitis C infection. ■ ■ ■

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The Mission of the Hepatitis C Support Project is to offer support to those who are affected by the hepatitis C Virus (HCV) and HIV/HCV coinfection.

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