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Extrahepatic manifestations associated with chronic hepatitis C

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Overview

THE nonhepatic disorders sometimes associated with chronic hepatitis C infection include 1) mixed cryoglobulinemia, 2) membranoproliferative glomerulonephritis, 3) sporadic prophyria cutanea tarda, and 4) lichen planus. Although the pathogenesis in several of these entities is unclear, some are mediated by immune complexes.

Mixed Cryoglobulinemia and Glomerulonephritis

A high frequency of liver disease is seen in patients with cryoglobulinemia. The recent discovery that over 80% of the sera from patients with type II mixed cryoglobulinemia contain HCV RNA by PCR suggests a direct role for this virus in the etiology and pathogenesis of this disorder. In contrast to this detection of HCV RNA, false-negative results have occasionally been observed for antibodies against HCV in patients with cryoglobulinemia presumably due to an atypical immune response to this agent or to the presence of immune complexes.

The diagnosis of cryoglobulinemia as a clinical entity depends on the proper collection of samples to obtain a cryocrit. Clinicians must work closely with the laboratory to ensure that phlebotomy tubes are prewarmed to approximately 37°C during collection of the blood, and that the blood is allowed to clot at that temperature. Serum placed in cryocrit tubes should be monitored for 72 hours at 4-8° C prior to centrifugation in the cold. Although cryoglobulin (or rheumatoid factor) is detected frequently (36-54%) in HCV-infected patients with chronic active hepatitis (± cirrhosis), only a few have evidence of systemic vasculitis.

The clinical manifestations of mixed cryoglobulinemia are generally those of systemic vasculitis caused by deposition of immune complexes. They include skin lesions (palpable purpura and urticaria), polyarthralgia, profound weakness, renal disease (proteinuria, nephrotic syndrome, hypertension and hematuria), peripheral neuropathy (paresthesias and numbness), and hepatic involvement. Decreased levels of complement are usually present. HCV RNA and anti-HCV have been detected in the cryoprecipitate at concentrations that are 10-to 1000-fold higher than those found in the serum. The glomerular immune deposits observed in membranous nephropathy may be caused by viral antigen-antibody complexes, by a tissue antigen released from cells infected with the virus, or by a neoantigen induced by the virus.

Alpha-interferon treatment of patients with HCV and mixed cryoglobulinemia has been effective in those instances when the virus burden has been markedly reduced or abolished. This provides further evidence of a causal association. In this situation, there is normalization or improvement of the ALT level, reduction of the cryoglobulin level, resolution of purpura and neuropathy, and recovery of renal function. However, the long-term efficacy often is disappointing since reactivation of the vasculitis usually occurs in patients who relapse following therapy.

Prophyria Cutanea Tarda

Type I porphyria cutanea tarda (PCT) is an acquired disorder manifested by photosensitivity and marked uroporphyrinuria and increased plasma prophyrin levels in patients with underlying liver disease. The fluorescence spectrum of plasma can distinguish variegate and erythropoietic protoporphyria from sporadic PCT. The marked increase in urinary uroporphyrin levels is what separates this disease from other hepatic porphyrias. While the disease is believed to be due to inactivation of hepatic uroporphyrinogen decarboxylase activity, which is responsible for a reduced conversion of uroporphyrinogen to coproporphyrinogen, alcohol abuse, hepatic siderosis,

drug toxicity (halogenated hydrocarbons), and HCV infection are important co-factors in the pathogenesis of this disease. Thus, the defect appears to be acquired and reversible.

The principal clinical manifestation in sporadic PCT is cutaneous photosensitivity (dermatitis) caused by activation of prophyrins that accumulate in the skin after exposure to long-wave ultraviolet light (UV-B) from the sun. This generates oxygen radicals that damage exposed fragile skin leading to erythema and the formation of vesicles (blisters) or bullae which may become infected. This may result in areas of hypo-or hyperpigmentation and to sclerodermatous changes. An increase in facial hair is common.

Most patients have liver disease which is relatively mild, although cirrhosis and hepatocellular carcinoma may occur. The frequency of anti-HCV increases with the severity of the liver injury and approaches 100% when moderate to severe chronic hepatitis is present. Thus, HCV is probably the principal cause of PCT-associated liver disease. Because of the accumulation of uroporphyrin in the liver, the tissue shows intense red fluorescence when exposed to ultraviolet light. Moderate siderosis is a conspicuous histologic feature in this disease and lipofuscin deposition is prominent.

In some cases, PCT remits when iron is removed from the liver by short-term phlebotomy (5 to 6 units of blood removed over 6 to 12 weeks). It also is reasonable to assume that successful treatment of HCV with alpha-interferon will result in remission of the clinical manifestations of PCT. If these treatments are not effective or feasible, low-dose chloroquine (125 mg twice weekly for several months) may be effective. In addition, patients should avoid offending agents such as alcohol and estrogens.

Lichen Planus

It has been reported that up to 90% of patients with lichen planus and chronic liver disease will have antibodies to HBV or HCV. Lichen planus presents as irregular, violaceous, glistening, flat-topped, pruritic papules covered with a thin, horny, adherent film. It often is distributed on the flexor surfaces of the wrists, forearms and legs. The skin lesions may be preceded by the appearance of grayish-white papules in the mouth, usually on the buccal mucosa which often present as a reticular network.

Sialadenitis

Although this disorder is relatively common in patients with chronic hepatitis C, it is usually mild, clinical manifestations and histologic lesions resembling Sjogren's syndrome sicca complex are rare, and specific autoantibodies (SS-A, SS-B) are uncommon. Similarly, only a small number of patients with Sjogren's syndrome are also infected with HCV and the incidence of liver dysfunction in Sjogren's syndrome is low.

Miscellaneous

In addition to the above conditions, HCV induces autoimmunity to GOR and LKM antigens. Other anti-tissue antibodies also are detected, especially in patients with chronic active hepatitis or cirrhosis. Such patients often exhibit higher globulin levels and an increased prevalence of extrahepatic immunological diseases (up to 16% in one series). A relationship between autoimmune thyroiditis (with its high prevalence of thyroid antibodies) and HCV infection has been observed by some investigators, but not by others. It has been suggested that the relatively high incidence of thyroid dysfunction (2 to 5%) detected during alpha-interferon therapy may be related to an exacerbation of previous latent thyroiditis. Although acute hepatitis C may cause transient bone marrow depression, several studies have shown that HCV (like HBV and HAV) is not responsible for hepatitis-associated aplastic anemia. Thus another viral agent (e.g., hepatitis G virus) or toxic metabolite must be considered in the causation of this disease.

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