Extrahepatic Manifestations of Chronic Viral Hepatitis

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Hepatitis B (HBV) and C (HCV) viruses are well-recognized causes for chronic hepatitis, cirrhosis, and even for hepatocellular carcinoma. Apart from liver disease, these viral infections are known to be associated with a spectrum of extrahepatic manifestations. The prevalence of clinically significant extrahepatic manifestations is relatively low, but it can be associated with significant morbidity and even mortality. An awareness and recognition of these manifestations is of paramount importance in facilitating early diagnosis and in offering treatment. However, treatments are not necessarily effective, and patients may continue with disabling extrahepatic manifestations. Hepatitis B virus has been well recognized as causing a variety of manifestations that include skin rash, arthritis, arthralgia, glomerulonephritis, polyarteritis nodosa, and papular acrodermatitis. More recently, infection with hepatitis C virus has elicited considerable interest for its role in a spectrum of extrahepatic manifestations. Among the best-reported are cryoglobulinemia, glomerulonephritis, high titer of autoantibodies, idiopathic thrombocytopenic purpura, lichen planus, Mooren's corneal ulcer, Sjögren's syndrome, porphyria cutanea tarda, and necrotizing cutaneous vasculitis. The precise pathogenesis of these extrahepatic complications has not been determined, although the majority represent the clinical expression of autoimmune phenomena.

Introduction

A wide spectrum of extrahepatic manifestations can be recognized in patients with chronic viral hepatitis B or C (Tables 1 and 2). The clinical presentation of these findings can occasionally be subtle and of unclear relationship to the viral infection, although a minority of these patients develops clinically significant and clearly associated extrahepatic manifestations. The prognosis of these conditions is variable. In addition, some patients may present with more than one of these manifestations. Although the pathogenetic mechanisms for these complications are not fully understood, autoimmunity triggered by viral invasion and replication in the affected tissues may have a major role. This assumption is supported by detection of epitopes of hepatitis C virus (HCV), such as E2 protein and viral RNA, in B-lymphocytes, monocytes, polymorphonuclear leukocytes, and various tissues [1].

Chronic Hepatitis B

Cutaneous manifestations

A variety of cutaneous manifestations have already been recognized, including hives and fleeting maculopapular rash during the early course of viral hepatitis. Women are more prone to developing cutaneous manifestations. The nature of these cutaneous lesions is that they are episodic, palpable, and at times pruritic. Although they are transient, a discoloration of the skin can be identified after the resolution of the exanthem, particularly on the lower extremities. Acropapular dermatitis, also recognized as Gianotti-Crosti syndrome, has been associated with hepatitis B virus (HBV) infection, more commonly with acute infection in children [2].

Polyarteritis nodosa

Clark *et al*. [3] reported the first association between viral hepatitis and arteritis in 1937, and the link with hepatitis B was first described in 1970 [4] when the presence of hepatitis B surface antigen (HBsAg) in serum and in the vascular lesions was reported. Evidence for a cause and effect relationship is further supported by a high prevalence of HBsAg in 36% to 69% of patients with polyarteritis nodosa (PAN) [5]. This very serious complication presents early during the course of the disease and has a high incidence among certain populations such as the Alaskan Eskimos. The pathogenesis of PAN is not clear. Circulating immune complexes containing HBsAg, immunoglobulins (IgG and IgM), and complement have been demonstrated by immunofluorescence in the walls of the affected vessels that might trigger the onset of the disease, although it is uncertain if these represent its primary etiology.

The clinical manifestations of the disease include hypertension (sometimes severe), pericarditis, heart failure, hematuria, proteinuria, renal insufficiency, abdominal pain, mesenteric vasculitis, arthralgias, arthritis, mononeuritis, and skin rashes. Significant proteinuria (>1 g/d), renal

Table 1. Extrahepatic manifestations of chronic hepatitis B virus infection

Polyarteritis nodosa
Glomerulonephritis
Essential mixed cryoglobulinemia
Rashes

insufficiency (serum creatinine >1.6 mg/dL), gastrointestinal involvement, cardiomyopathy, and central nervous system involvement are associated with increased mortality [6]. The course of PAN is independent of the severity and the progression of the liver disease. Twenty percent to 45% of these patients will succumb as a consequence of vasculitis within 5 years despite treatment, and the mortality rate is similar for HBsAg seropositive and seronegative patients with PAN [7,8].

Small- and medium-sized arteries and arterioles are affected. Fibrinoid necrosis and perivascular infiltration containing mononuclear and polymorphonuclear leukocytes are the major findings. Acute lesions are found in small arteries, and chronic changes (focal or diffuse fibrous replacement of the media and obliteration of the lumen) are observed in medium-sized arteries. Biopsy of a lesion may not be representative of the magnitude of the disease due to the patchy nature of the disease.

Various types of treatment, including corticosteroids, antiviral agents, immunosuppressive agents, and plasmapheresis, have been utilized for this serious presentation. Although corticosteroids and immunosuppressive agents may be beneficial in treating vasculitis, they may have a deleterious effect on the course of HBV liver disease due to viral reactivation, particularly after the withdrawal of treatment [9,10]. Adenine arabinoside, an antiviral drug, and interferon alfa (IFN-α), an immunomodulator and antiviral protein, have been used in conjunction with plasmapheresis and a short course of corticosteroids, with promising results [7]. Because this is a rare complication, no published reports are available for the newer therapies for HBV, which include the nucleoside analogue lamivudine.

Glomerulonephritis

The first report associating chronic HBV infection with renal disease was published in 1971 by Combes *et al*. [11]. These authors demonstrated the presence of immunocomplexes of HBsAg with antibodies and complement components such as C3 in a patient who developed post-transfusion hepatitis B complicated by severe proteinuria, hypoalbuminemia, and edema. The most common type of glomerulonephritis described is membranous (MGN), which exists mainly in children, but membranoproliferative (MPGN) and, even more rarely, IgA nephropathy have also been identified. The prevalence of glomerulonephritis among patients with chronic HBV infection is not well known, although observations made in children suggest that it is between 11% (in a Japanese population) and 56% (in a study from Poland) [12,13]. Such a high prevalence, however, is not recognized in the United States, and this may be because of the differences in epidemiology of HBV, which might be predominantly perinatal in other geographic areas.

Clinical, biochemical, and serologic features

The clinical presentation of glomerulonephritis includes fatigue, pallor, edema, and weakness. Hypoalbuminemia (to as low as 1 g/dL) and hypercholesterolemia may be seen. Heavy proteinuria (2 to 20 g/d), along with an active urine sediment, is usually observed. In childhood, significant renal failure is uncommon, and its presence should raise the suspicion of another etiology of glomerulonephritis. A previous history of chronic liver disease is not present in the majority of these patients, and most of them have no clinical or biochemical findings to suggest acute or chronic liver disease [14,15]. However, liver biopsies often demonstrate features of chronic hepatitis. Serologic markers of an HBV replicative state are often evident, and complement activation is suggested by low levels of C3 and C4.

Histologic features

Histologically, several lesions have been identified, but three distinctive morphologic lesions are most often recognized: MGN, MPGN, and IgA nephropathy. Patients may have one distinct histologic lesion or have overlapping features in a single kidney biopsy. The predominance of a particular lesion may depend upon the qualitative and quantitative differences in the immune complexes formed. Generally, the most prominent finding among children is that of MGN with, mainly, capillary wall deposits of HBeAg. Adults, in contrast, present with features of MPGN with mesangial and capillary wall deposits of HBsAg. A rare overlap between membranous nephropathy and IgA nephropathy has also been described [16].

Pathogenenesis

The mechanism by which patients with chronic HBV develop glomerulonephritis is not completely understood. One possible explanation is that HBV antigens (HBsAg and HBeAg) act as triggering factors eliciting immunoglobulins and thus forming immune complexes, which are dense, irregular deposits in the glomerulocapillary basement membranes [16]. It is known that immune complexes of less than 1 million daltons, such as those initiated by HBeAg, can cause renal complications. Therefore, it is not unusual for HBV infection to initiate renal disease, given the molecular weight of HBsAg of more than 3 million daltons [17].

HBV DNA has been identified by in situ hybridization (ISH) in the kidney specimens, distributed generally in the nucleus and cytoplasm of epithelial cells and mesangial cells of glomeruli, and in the epithelial cells of renal tubules [18]. HBV DNA may also exist simultaneously in the renal interstitial tissues. The positive results for HBV

Table 2. Extrahepatic manifestations of chronic hepatitis C virus infection

Nonspecific autoantibodies
Essential mixed cryoglobulinemia
Glomerulonephritis
Lichen planus
Porphyria cutanea tarda
Leukocytoclastic vasculitis
Mooren's corneal ulcer
Non-Hodgkin's lymphoma
Polyarteritis nodosa
Autoimmune thyroiditis
Diabetes mellitus
Sjögren's syndrome

DNA by ISH have correlated well with HBV antigen assays. The more extensive the presence of HBV DNA in the nephron unit and interstitial tissue, the more severe the renal manifestation. Finally, the duration of proteinuria in patients with HBV DNA in renal tubules has been much longer than in those with no HBV DNA in renal tubules.

Treatment

Immunosuppressive therapy for HBV glomerulonephritis has generally failed to induce remission, although a few patients may have an incomplete response. Furthermore, such therapy raises the risk of reactivating HBV infection, particularly when given for a short course [17]. Therapy with interferon alfa has been successful in HBV-related glomerulonephritis. A regimen of 5 million units of subcutaneous IFN-α, given daily for 4 months, has achieved HBsAg seroconversion with improvement of glomerulonephritis [19•]. It was also reported that IFN-α, given at a dosage of 3 million units three times a week, led to improvement of proteinuria in patients with mesangial proliferative glomerulonephritis [20•] but not in patients with MPGN. Finally, a single case report describes the resolution of this complication after liver transplantation [21].

Prognosis

The prognosis of the disease is related to several factors such as age and response to therapy. Children with MGN respond more favorably than do adults. Whites respond better than Asians and Blacks. Approximately 30% to 60% of patients with MGN have a spontaneous remission. However, the course of HBV-related membranous nephropathy in adults in areas where HBV is endemic is not benign. Regardless of treatment, the disease has a slow but relentlessly progressive clinical course in approximately one third of patients, who ultimately have progressive renal failure necessitating maintenance dialysis therapy [22].

Essential mixed cryoglobulinemia

Essential mixed cryoglobulinemia (immunoglobulins precipitating reversibly in a cold environment) is a systemic disease that can be initiated by the presence of HBV. Liver involvement is evident at presentation in 32% of patients with essential cryoglobulinemias. There are three types of cryoglobulins, depending on the immunochemical classification. Type II (monoclonal IgM and polyclonal IgG) and type III (polyclonal IgM and polyclonal IgG) are classified as essential and can be found in patients with chronic HBV infection. The prevalence of this complication in HBV infection has ranged between 0% [22] and 15% [23]. Purpura is the most common presenting feature, followed by arthralgias. Renal involvement has been described. Neurologic impairment is a less frequent finding in patients with chronic liver disease. In contrast, Raynaud's phenomenon, arthritis, and sicca syndrome are more frequent. The clinical symptomatology is present in approximately 25% of patients with serum cryoglobulinemia. This complication is more commonly found in patients with a longer duration of HBV infection, higher levels of gamma globulin, and cirrhosis [22]. The differences between vasculitis induced by cryoglobulins and polyarteritis nodosa are that the former affects only small size vessels, is not associated with peripheral eosinophilia, and includes no aneurysm formation. The role of antiviral treatment has not been extensively evaluated, although there are data showing that IFN-α has been somewhat beneficial [24].

Chronic Hepatitis C

Nonspecific autoantibodies

A variety of circulating autoantibodies, often at low titers, can be identified in patients with chronic HCV infection. The presence of autoantibodies is seen at least three times more often than the incidence of clinical autoimmune disease [25•]. Rheumatoid factor is the most frequently detected marker (30% to 76%) among patients with chronic HCV infection. Antinuclear and anti–smooth-muscle antibodies at a low titer (1:40 to 1:80) can be found in 32% and 11% of patients with chronic HCV, respectively. Antibodies to liver/kidney microsome type I (anti-LKM) are the most characteristic in patients with type II autoimmune hepatitis. Approximately 1% of adult HCV patients in the United States are anti–LKM–positive. Conversely, 50% to 86% of anti-LKM–positive patients have anti-HCV [26,27••]. Antibodies to GOR can be identified in 81% of these patients. Anti-GOR can be detected early during acute HCV infection, even before the development of anti-HCV. It has been observed that

patients with high titers of this marker may have more severe chronic hepatitis; the levels of anti-GOR are reduced after successful treatment with interferon alfa [28]. Generally, autoantibody production has not been associated with any particular HCV genotype, but some evidence indicates that patients infected with genotype 3 have a lower prevalence of anti-SMA and ANA.

Essential mixed cryoglobulinemia

A clear relationship between HCV and essential mixed cryoglobulinemia (EMC) types II and III has been established. The prevalence of this complication ranges from 10% to over 50%. Some of the factors influencing this wide range are the index of suspicion and the detection capabilities of the various laboratories in identifying the cryoglobulins. Guidelines for the collection of blood must be rigorously followed. The patient must be fasting, and 20 cm^3 of blood must be obtained. This specimen must be placed in a tube without anticoagulant and maintained at a temperature of 37° C until it coagulates. Thereafter, it must be centrifugated, and the serum must be stored at 4° C for 7 days for the presence of cryoprecipitate. At this time, the cryocrit must be tested by reheating the specimen and then by immunodiffusion. When cryoglobulins are properly determined, the prevalence of anti–HCV and HCV RNA in patients with EMC ranges between 42% and 90% [29,30]. The pathogenesis of EMC in chronic HCV-infected patients appears to be multifactorial, although the stimulation of B cells with subsequent clonal expansion and immunoglobulin (IgM) production is one of the major mechanisms. Cryoglobulins consist of an antibody complex, in which HCV RNA and viral antigens bind to IgG antibodies, which in turn bind to an IgM with anti-IgG properties [31]. These complexes precipitate in the walls of small- and medium-sized vessels, producing lesions that are compatible with leukocytoclastic vasculitis. It is not uncommon for patients with high cryoglobulin levels to have negative results for serum HCV RNA because the genome of the virus may be trapped in the precipitate [32].

Most patients with chronic hepatitis C who have circulating cryoglobulins are asymptomatic, and only a minority (approximately 10%) develop clinical manifestations of this complication. Female patients, with a longer duration of HCV infection, and particularly with higher age, are more prone to develop clinical findings of this entity. EMC has also been described after orthotopic liver transplantation for HCV-related liver disease. No strong correlation has been shown between HCV genotypes and EMC, although reports from Italy emphasize that HCV patients infected with genotype 2 have a higher prevalence of EMC [33]. Furthermore, it was recently shown that patients carrying the haplotype HLA B8, DR3 are more susceptible to developing EMC [34]. Interferon, alone or in combination with ribavirin, has been the mainstay for treatment, although 50% of patients treated with interferon alone will have symptomatic relapse after discontinuation of treatment [35].

Glomerulonephritis

Epidemiologic evidence suggests that HCV infection may be a major risk factor for both cryoglobulinemic and non-cryoglobulinemic membranoproliferative glomerulonephritis and membranous glomerulonephritis.

Cryoglobulinemic glomerulonephritis

The estimated prevalence of renal involvement in patients with EMC is around 50%, and the prognosis is not favorable [36]. Patients usually present with features of nephrotic syndrome. Microscopic hematuria and proteinuria are the most common manifestations. Mild renal insufficiency can be present. The principal histopathologic lesion is an increase in the cellularity and accentuation of the lobular architecture of the glomerular tuft. Mesangial proliferation and sclerosis can also be identified. Immunofluorescence techniques reveal mesangial and capillary wall deposition of IgM, IgG, and C3 in most patients. Electron microscopic findings include subendothelial deposits characteristic of MPGN despite the fact that mesangial and subepithelial immune deposits are only occasionally found. In addition, the immune deposits have ultrastructural characteristics of cryoglobulins (Fig. 1). Serology reveals hypocomplementemia with low levels of CH 50, C4, and C3. The C4 fraction of complement is markedly decreased in comparison with that of C3.

Interferon alfa, alone or in combination with ribavirin, appears to improve the clinical features of the disease. Unfortunately, many patients may experience a relapse after discontinuing therapy. A preliminary report has suggested a beneficial effect from ribavirin alone [37]. However, caution needs to be exercised in using ribavirin in these patients because underlying renal insufficiency may predispose them to profound hemolytic anemia.

Non-cryoglobulinemic glomerulonephritis

Some patients with chronic HCV may develop features of nephrotic syndrome or non-nephrotic proteinuria and renal insufficiency without signs or symptoms of cryoglobulinemia. The renal histopathologic features for this group of patients are those of membranoproliferative or acute proliferative glomerulonephritis. Patients who developed this complication and received interferon alfa for 6 to 12 months had a significant reduction in proteinuria but no improvement in renal function [38].

Membranous glomerulonephritis

Although membranous glomerulonephritis represents the most common type of glomerulonephritis in patients with chronic HBV infection, its prevalence is low among

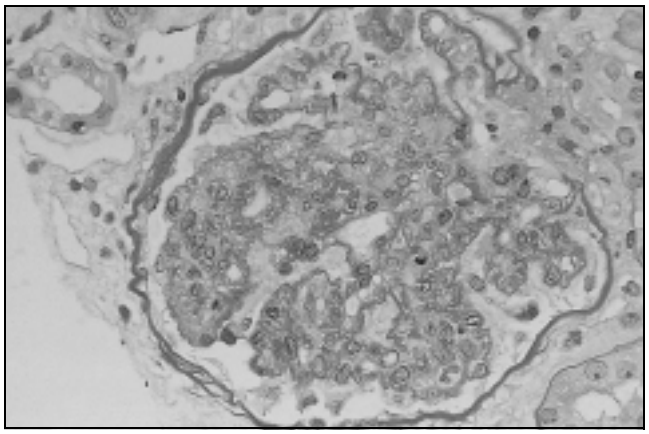

Figure 1. Glomerulus demonstrating an increase in the cellularity and accentuation of the lobular architecture of the glomerular tuft. Lesions are compatible with membranoproliferative glomerulonephritis.

patients infected with HCV who have renal involvement. The pathogenesis of this complication is not fully understood, but it is speculated that patients with chronic HCV infection may develop membranous glomerulonephritis through immune complex deposition involving HCV proteins [39]. HCV RNA has also been isolated from renal biopsy specimens. Treatment with interferon alfa can improve the renal function of these patients [40].

Cutaneous manifestations

A number of dermatologic abnormalities have been described as extrahepatic manifestations of HCV.

Cutaneous vasculitis

Palpable purpura and petechiae, primarily of the lower extremities, are the most common clinical findings of cutaneous vasculitis. Cryoglobulins, high levels of rheumatoid factor, and low levels of C3 and C4 can be identified. Deposition of immune complexes in the vessel wall and activation of complement appear to be the triggering factors. Skin biopsy of these lesions often reveals narrowing of the vessel lumen, destruction of the small blood vessels, inflammation with polymorphonuclear cells, and findings compatible with leukocytoclastic vasculitis. Although HCV antigens have been found in keratinocytes and within the vessel walls, the triggering mechanism for the vasculitis is unclear. These lesions appear to respond to IFN-α therapy, although aggravation of the symptomatology has been reported [41].

Lichen planus

Rebora *et al*. [42] reported the first association between lichen planus (LP) and chronic liver disease in 1978, and Mokni *et al*. [43] described the association between LP and HCV in 1991. The major characteristics of LP are violaceous, scaling angular papules, usually located on the flexor areas of the limbs, and white reticular lesions on the mucous membranes and the genitalia. Oral manifestations can be found in the absence of skin lesions. It has been hypothesized that this disease represents an autoimmune response to basal cell antigens or a hyperimmune response to antigens shared by basal cells and a viral antigen. Histologic findings such as local infiltration of activated T lymphocytes in the upper dermis raise the suspicion that a T cell–mediated reaction to an epitope shared by basal cells and HCV might be the triggering factor for this disease. The prevalence of LP among HCV-infected patients has been estimated at about 5%, whereas the prevalence of anti-HCV in patients with LP has been estimated to be as high as 38%. IFN-α treatment can improve this clinical manifestation, but it has also been reported to aggravate it [44•].

Porphyria cutanea tarda

Porphyria cutanea tarda (PCT) is the most common type of porphyria. It is caused by decreased activity of the enzyme uroporphyrinogen decarboxylase. There are two forms of the disease: familial and sporadic. The major features are cutaneous lesions such as vesicles, bullae (frequently noticed after sun exposure) increased skin fragility, pigmentation, and hirsutism (Fig. 2). Several factors, including alcohol, estrogens, and iron overload, have been implicated in the clinical expression of PCT. It is speculated that HCV can also activate the expression of PCT, and the seroprevalence of anti-HCV in these patients ranges from 62% to 100%. There is a higher frequency of immunologic alterations in HCV patients with PCT, which includes high titers of ANA, ASMA, anti-GOR, cryoglobulins, anti-LKM1, and RF. In Europe, a north-to-south gradient has been established for the association of HCV and PCT, with a higher prevalence being in the south. In a study from Spain, 45% of PCT patients were found to be HCV RNA–positive by serum, and 100% were HCV RNA–positive by liver biopsy specimens [45]. IFN-α, in conjunction with phlebotomy (the traditional treatment of PCT), may be beneficial for these patients.

Polyarteritis nodosa

In one study, 20% of the patients with polyarteritis nodosa (PA) were anti-HCV–positive, but only 5% were HCV RNA–positive. HCV may play a role in the pathogenesis of this entity, but additional studies are needed to validate this observation [46].

Additional cutaneous lesions

Some additional manifestations that might be related to HCV include erythema nodosum, erythema multiforme, urticaria, Adamantiades-Behçet syndrome, and vitiligo.

Ocular manifestations

Mooren's corneal ulcer is a chronic progressive unilateral or bilateral peripheral ulcerative keratitis that can be associated with chronic HCV infection. IFN-α is the treatment of choice, although relapse has been noted after completion of treatment. It has been suggested that all patients with

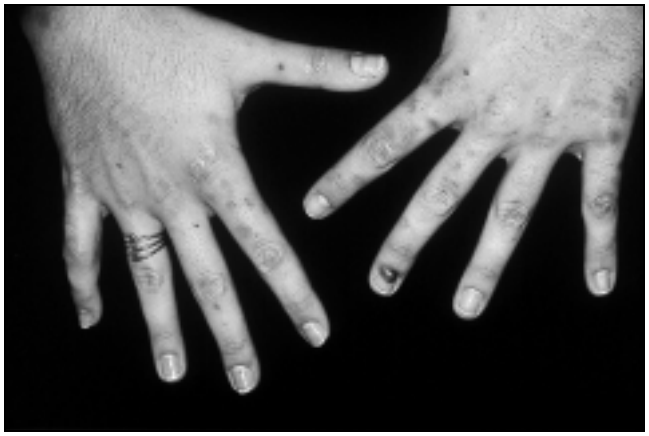

Figure 2. Blistering and bullous eruption of the hands, as depicted here, is compatible with porphyria cutanea tarda.

Mooren-type ulcers should be tested for evidence of HCV infection. Even if improvement is obtained during treatment, continued follow-up is mandatory because relapse is common and repeated treatment may be effective [47].

Lymphoproliferative disorders

The relationship between EMC and non-Hodgkin's B-cell lymphoma has been established. The latter disorder seems to be related to HCV lymphotropism, which could also be responsible for the evolution of EMC to malignant lymphoma. In addition, HCV infection may be involved in the pathogenesis of idiopathic B-cell non-Hodgkin's lymphoma through a similar pathogenetic mechanism [48]. A relationship between HCV and lymphoplasmatocytoid immunocytomas has also been reported. Replicating HCV has been identified in the cytoplasm of hepatocytes and lymphoid aggregates, and in the bone marrow of patients with this diagnosis. IFN-α can be effective therapy because it reduces cryoglobulins, thereby preventing the development of non-Hodgkin's lymphoma [49•].

Sjögren's syndrome

EMC is frequently associated with Sjögren's syndrome, and reports suggest an association between this syndrome and HCV. Fourteen percent to 57% of patients with chronic hepatitis C may have features of lymphocytic sialadenitis in a labial salivary gland biopsy. HCV has been found in saliva, and a direct cytopathic effect or an indirect immune-mediated phenomenon might be pathogenetically responsible. In addition to sialadenitis, 25% of patients have moderate xeropthalmia [50].

Endocrine disorders

In patients with HCV infection, a high prevalence (20% to 30%) of autoantibodies against the thyroid gland, such as antibodies against thyroglobulin, thyroid microsomes, and thyroid peroxidase, has been reported. An increase in the titer of these autoantibodies has also been noticed during treatment of chronic hepatitis C. Some patients develop features of autoimmune thyroiditis (primarily hypothyroidism) during treatment [51].

An association between type II diabetes and HCV has also been reported. Genotype 2a has been found in a large number of cases, but this observation needs further investigation [52••].

Neuropathy

Peripheral neuropathy is found in patients with features of cryoglobulinemia-induced vasculitis. Initial symptoms are paresthesias, painful dysesthesias, and moderate motor weakness of the lower extremities. Subsequent progression of the manifestations is characterized by an asymmetric sensory axonal polyneuropathy or a multifocal neuropathy. A nerve biopsy demonstrates axonal neuropathy with a decrease in myelinated fibers [53].

Miscellaneous

Only a remote (if any) correlation exists between HCV and idiopathic pulmonary fibrosis, dilated cardiomyopathy, thrombotic phenomena due to antiphospholipid syndrome, and aplastic anemia.

Conclusions

Hepatitis B and C viruses are well known to cause chronic hepatitis and cirrhosis. It is important to remember that these infections can also cause—although infrequently—severe extra hepatic manifestations that are associated with significant morbidity and mortality. Because of the higher prevalence of chronic hepatitis C virus infection, compared with hepatitis B infection, we are more likely to encounter clinical conditions related to the former. Cryoglobulinemia, glomerulonephritis, and cutaneous manifestations are the best recognized extrahepatic manifestations of hepatitis C infection and are treatable to varying degrees. One hopes that better, more effective treatments for hepatitis C will be available in the future.

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