Hepatitis C virus infection: the dermatological perspective

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SUMMARY

The hepatitis C virus (HCV) is the most common causative agent of post-transfusion non-A, non-B hepatitis. At present, HCV infection is a major public health problem all over the world with a global prevalence of 3%. It is responsible for 70% of cases of chronic hepatitis, the major cause of cirrhosis and the most common cause of hepatocellular carcinoma. HCV-related end-stage cirrhosis is the main reason for liver transplantation. 70-85% of mostly inapparently infected patients develop chronic infection which is generally asymptomatic. Within 20 years of infection cirrhosis may develop in 20% of them. The annual incidence of hepatocellular carcinoma is 1-4%.The current treatment of chronic hepatitis C is the combination of interferon alpha and ribavirin with the sustained treatment response range of 56-82%. Chronic hepatitis C is associated with a host of extrahepatic manifestations, many of which are cutaneous. These may be arbitrarily divided into commonly associated (mixed cryoglobulinemia, porphyria cutanea tarda), associated (lichen planus, Sjögren's syndrome) and other less common conditions being reported in association with HCV. Screening for HCV in the »silent pool« of infected may prevent the development of terminal, life-threatening consequences and further transmission of HCV.

KEY WORDS

hepatitis C, mixed cryoglobulinemia, porphyria cutanea tarda, lichen planus, Sjögren's syndrome

Introduction

Hepatitis C virus (HCV) was identified in 1989 as the causal agent of most cases of posttransfusional and sporadic non-A, non-B hepatitis (1). At present, HCV infection is a major public health problem all over the world with a global prevalence of 3% (170 million of infected), with 3-4 million people being newly infected each year (2). The seroprevalence rate is ranging from 1% in Western Europe and North America, 3-4% in some Mediterranean and Asian countries up to 10-20% in parts of central Africa and Egypt (3). The prevalence seems to be higher in Eastern Europe than in Western Europe.

In industrialised countries, HCV accounts for 20% of cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of hepatocellular carcinoma and 30% of liver transplants (4). However, the future burden of hepatitis C is going to be even more dramatic. Global estimates have suggested that by the year 2008, the cases of liver cirrhosis

will increase by 528%, hepatocellular carcinoma by 279%, and liver disease-related deaths by 223% (5). One of the most important actions to prevent the uncontrolled damage is early diagnosing that leads to effective follow up and treatment. Cutaneous manifestations may be the first signs of HCV infection.

The hepatitis C virus infection

The virus and its pathogenesis

Hepatitis C virus is a member of the *Flaviviridae* family, which includes the classical flaviviruses and the animal pestiviruses. The structure and the replication cycle of HCV are incompletely understood. The virion contains a positive single-stranded RNA genome of 9.5 kilobases which consists of 5' and 3' untranslated regions important for translation of viral proteins and replication of the virus. HCV replication is a highly dynamic process with a viral half-life of only a few hours and average daily virion production and clearance rates of 10^{12} and more which provides the basis for genetic variability of HCV (6). This findings are similar to the dynamics of HIV infection. There are at least 6 genotypes and more than 50 subtypes of HCV with the genotypes *1*, *2*, and *3* distributed world-wide (70-80% prevalence of genotype 1 in most Western countries), genotypes *4* and *5* distributed predominantly in Africa and genotype *6* found primarily in Asia.

Hepatitis C virus infection leads to viral persistence and chronic hepatitis in a very high proportion of infected by an immune escape mechanism despite broad activation of potent humoral and cellular immunological responses to viral proteins (7). These responses may be thwarted by the high rate of mutations, which leads to the generation of a highly variable mixture of closely related genomes that persist and continuously evolves in infected individuals.

HCV appears to be minimally cytopathic, therefore the immune response against HCV plays a central role in HCV pathogenesis (8). Liver damage in chronic hepatitis C is mostly due to host immune-mediated responses, including cytosine secretion by CD4+ cells and CTL-induced cell death through direct cell-to-cell interactions and cytosine secretion. Moreover, patients with HCV infection frequently have autoimmune diseases and circulating tissue-specific and non-specific autoantibodies (9, 10).

Modes of transmission

Hepatitis C virus is primarily spread by direct contact with infected blood (11). With the introduction of anti-HCV screening programmes of blood and blood products the new cases of posttransfusion hepatitis have virtually disappeared and intravenous drug use has become the major identifiable mode of transmission in many countries. Intranasal cocaine use, non-professional tattooing and piercing have become identified as possible modes of transmission (12). Nosocomial transmission has been reported in dialysing units (13). Occupational needlestick injuries from anti-HCV sources result in seroconversion in 2-8% of recipients (14).

Sexual transmission is possible but rare and correlates with high-risk sexual practices. The frequency of sexual transmission is estimated to approximately 5%, whereas for HIV it is 10-15% and for HBV 30% (15, 16). Coinfection with HIV increases the risk of sexual transmission of HCV.

Mother-to-infant transmission has been observed with the risk below 5%, unless the mother is co-infected with HIV (17). Hepatitis C virus transmission by breast feeding is unusual. Household transmission is uncommon (18). However, in up to 30-50% of patients with hepatitis C no epidemiological risk factor can be identified.

Natural history of hepatitis C

The infection with HCV is usually followed by a clinically completely inapparent hepatitis. Only 25% of patients are symptomatic and aware of the infection (19). One of the most striking clinical features of hepatitis C is its progression to chronicity in 70-85%. Only 25% of chronically infected have an asymptomatic infection with persistently normal liver tests. Typically, the majority of patients with chronic hepatitis C have few if any symptoms which are usually non-specific and mild, fatigue being the most common. Hepatitis C is a disease with various rates of progression. About 20% of patients with chronic hepatitis C will develop liver cirrhosis within approximately 20 years and may die of complications of cirrhosis in the absence of liver transplantation; the rate of hepatocellular carcinoma is 1-4% per year. A number of extrahepatic diseases and manifestations, associated to chronic hepatitis C (renal, cutaneous, rheumatoid, etc.), possibly representing the first clinical sign of HCV infection, have been reported (20).

Diagnosis and treatment

Diagnosis of hepatitis C is based on serological assays (a screening enzyme-linked immunosorbent assay and a confirmatory recombinant immunoblot assay) which detect HCV-specific antibodies (anti-HCV) and on molecular assays (polymerase chain reaction, PCR) which detect HCV RNA. Serological assays are used for screening and epidemiological surveillance. Active infection is confirmed by the presence of viral genome, detected by

a qualitative PCR; the quantitative PCR test is used to monitor disease activity and response to treatment.

The treatment of chronic hepatitis C is rapidly evolving. Extensive research and studies are undergoing to develop a more successful therapy. Currently recommended is the combination of interferon alpha and nucleoside analogue ribavirin (4). Recently, significantly increased response rates as compared to conventional interferon alpha have been achieved with polyetilenglycol (PEG)-conjugated interferon alpha (21, 22). Several factors contribute to the treatment response. The sustained virological response to the combination treatment including PEG interferon alpha has been achieved in 42-46% of genotype *1* patients and in 76-82% of genotypes *2* and *3* patients (23, 24). Side effects of interferon alpha are numerous and severe and require discontinuation of therapy in 2-10% of patients. The early side effects involve the inconvenience of subcutaneous administration of the medicine three times (or once) weekly for 6-12 months. The latter are variable and mostly caused by autoimmunity.

Dermatological manifestations of hepatitis C

Chronic hepatitis C is associated with a host of extrahepatic manifestations, many of which may be seen by dermatologists (25). Most of these are presumed to be immune mediated as a result of viral-dependent proliferation of monoclonal or polyclonal lymphocytes. Cutaneous manifestations appear to be mostly due to the deposition of circulating immune complexes in the skin or to the tissue deposition of specific T lymphocytes. In most cases, the details of pathogenesis of these disorders remain uncertain.

Cutaneous manifestations of chronic hepatitis C may be arbitrarily divided into three groups: often associated (mixed cryoglobulinemia, porphyria cutanea tarda, leukocytoclastic vasculitis, livedo reticularis), associated (lichen planus, Sjögren's syndrome, urticaria, pruritus, polyarteritis nodosa) and uncommonly associated (erythema nodosum, erythema multiforme, vitiligo, psoriasis, unilateral nevoid teleangiectasia, pyoderma gangrenosum, Behçet's syndrome, Mooren corneal ulcer, granuloma annulare, disseminated superficial actinic porokeratosis) conditions (26).

Mixed cryoglobulinemia

Cryoglobulinemia is commonly seen in patients with HCV infection. It is an immunologic disorder characterised by the presence of serum immune complexes, which precipitate at cold temperatures. Clinically it is characterised by systemic vasculitis with variable manifestations. There are three main types of cryoglobulinemia. It has been established that about 80% of type II (a polyclonal IgG component and a monoclonal IgM component) and type III (a polyclonal IgM and IgG components), so called mixed cryoglobulinemia occurs in patients with HCV infection (27). Since the initial observations in 1990, several reports have described mixed cryoglobulinemia in about 50% of patients with chronic hepatitis C (28, 29). Patients with cryoglobulinemia had cirrhosis more often and had a longer history of hepatitis than those without cryoglobulinemia (30).

One of the hypothesis for the cause of mixed cryoglobulinemia is the chronic stimulation of the immune system by a variety of infections, including HCV. Hepatitis C virus RNA sequences and HCV antibodies have been found in sera and in cryoprecipitates (31). By immunohistochemical or in situ hybridisation methods, HCV has been found in association with IgM and IgG in the cutaneous vasculitic lesions (32). One possible mechanism is that antigen-antibody complexes of viral particles and anti-HCV antibodies might be linked with rheumatoid factor activity directed to anti-HCV antibodies. Immune complexes initiate activation of endothelial cells, alter the vascular permeability, lead to neutrophyl infiltration and damage the vessel wall. An alternative mechanism was suggested by the finding of HCV in vascular endothelial cells: antibodies or T-cells sensitised to HCV may initiate the process.

The treatment for chronic hepatitis C is the therapy of first choice for patients with mixed cryoglobulinemia and HCV infection leading to the great improvement in the manifestations of cryoglobulinemia (27).

It is advised to screen the patients with mixed cryoglobulinemia for the presence of anti-HCV.

Porphyria cutanea tarda

Porphyria cutanea tarda (PCT) is the most common form of porphyria (33). There are two primary types of PCT: the familiar, inherited type and the acquired type that result from depletion of one of the enzymes in the porphyrin pathway, usually uroporphyrinogen decarboxylase. Clinically it presents as tense bullae, vesicles and erosions that heal with scarring and millia. The findings are seen on sun-exposed skin and patients complain of skin fragility rather than sensitivity to sunlight. The specific laboratory findings typical of PCT are the marked hepatic overproduction of uroporphyrins and heptacarboxyl porphyrins. Decreased activity of the enzyme uroporphyrinogen decarboxylase is an essential feature of the biochemical abnormalities of PCT. Among several major risk factors for development of PCT is also chronic liver disease. In addition to the well known association of alcoholic liver disease with PCT, studies reported have made chronic hepatitis C as an important trigger for development of PCT. Hepatitis C virus probably acts as a non-specific factor that reveals the deficit of uroporphyrinogen decarboxylase in a

genetically determined individual. Increased porphyrin in the skin triggers a phototoxic reaction and consequently stimulates collagen synthesis, which may result in sclerodermoid lesions in some patients (34).

A strong association (50-90%) has been demonstrated between sporadic PCT cases and HCV infection in patients from the Mediterranean basin, Japan and the United States (35-37). In other countries the prevalence is much lower (38, 39). Some cases of hepatocellular carcinoma complicating PCT may also be linked to HCV infection.

The initial management of PCT is vigorous iron removal; the next step in cases of HCV infection is the treatment of chronic hepatitis C with interferon-based therapies.

It is recommended that all patients with PCT should be screened for HCV infection.

Lichen planus

Lichen planus (LP) is a common mucocutaneous inflammatory disorder of uncertain aetiology, that can arise also in association with chronic liver disease. In 1991, LP was described in a patient with chronic hepatitis C (40). Since then, both mucosal and cutaneous lichen planus have been reported to occur in settings of chronic HCV infection, mostly based on seroepidemiological arguments (41, 42). The reported prevalence of HCV infection in patients with LP show wide variations, from 3.8% in France to 62% in Japan (43, 44). It has been reported that 2.4% to 8% of patients with chronic HCV related liver disease had oral LP (45). In one of the latest Italian studies the prevalence of oral LP in HCV positive patients was age-specific (46). There does not appear to be difference in prevalence of HCV between erosive and nonerosive forms of LP (47).

In our own study performed at the Clinic for Infectious Diseases and Febrile Illnesses and Department of Oral Medicine and Periodontology, both at the University Medical Centre, Ljubljana, among 50 patients with chronic hepatitis C there were 7 having oral LP (14%) (48).

In one of our previous studies we reported the presence of HCV RNA in gingival crevicular fluid which might have possibly reflected the viral presence in mucosal epithelial cells (48). In a recent study, HCV RNA was demonstrated in LP lesional skin biopsies (49). Encouraged by the epidemiological studies on striking association between oral lichen planus and chronic HCV infection, Arrieta et al. had demonstrated by *in situ* hybridisation that HCV replicates in oral mucosal epithelial cells from patients with chronic hepatitis C with and without oral lichen planus (50). The pathological consequences of this finding remain to be elucidated.

The aetiology of oral lichen planus is unknown and may be caused by a cell-mediated immunological response to induced antigenic changes in mucosal epithelium (51). It may be hypothesised that HCV infection may induce autoantibodies against the product of a host gene termed GOR which shares several amino acids with the core gene product of HCV (52). It is assumed that although HCV is not the primary cause of LP *per se*, it may play a pathogenic role by triggering LP in genetically succeptible HCV-infected patients (49).

The treatment with interferon alpha more often than not results in the eruption or aggravation of lesions. Lichen planus may therefore have a different clinical behaviour in patients with HCV infection and/or interferon treatment, hypothesising a role of HCV and/or interferon in the modulation of host/immune response (46).

The role of HCV in LP remains unclear. It appears that there may be geographical differences in the association between HCV infection and LP.

Sjögren's syndrome

Sjögren's syndrome (SS) is an autoimmune disease of unknown aetiology, although viral infections being implicated in its development (53). A possible relationship between SS and HCV infection was postulated in 1992. The prevalence of antibodies to HCV infection in patients with primary SS ranges between 14 and 19% (53). Chronic HCV infection may mimic the main clinical, histological and immunological features of "primary" SS. It has been suspected that lymphocytic capillaritis related to HCV infection could represent an early stage of more severe lesions resembling the lymphocytic sialadenitis of SS.

Most of the current studies suggest a direct role of the viral proteins in the pathogenesis of sialadenitis in some patients with chronic HCV infection (53). Most recently, by using the *in-situ* hybridisation, HCV replication was demonstrated as well in epithelial cells from salivary gland of patients with SS (54).

The estimated prevalence of definite SS in Slovenia is 0.60% (55). In our previous study of patients with chronic hepatitis C, the questions on possible oral involvement in SS were simply raised without performing other tests necessary for diagnosing SS (48). None of the patients enrolled answered positive to this particular questions.

Testing for HCV infection is advised to be performed in patients with SS, especially in those patients with evidence of liver involvement or associated cryoglobulinemia.

Other manifestations

Various other skin diseases have also been described with HCV infection: acute and chronic urticaria (56, 57), pruritus and prurigo (58), polyatreritis nodosa (59), vitiligo, psoriasis (60), and many others (61). However, epidemiological studies are needed being essential to

determine the real prevalence of these dermatoses in HCV infection.

In addition, a variety of skin manifestations may be related to the therapy with interferon alpha, the most common of which are erythema at sites of injection, transient alopecia (in 25%), dry skin (in 8-13%), acne, nail disorders and some others. Therapy can also exacerbate other autoimmune disorders, including psoriasis.

Conclusion

Cutaneous manifestations may be the first clinical sign of chronic HCV infection. In view of rapidly evolving follow up and therapeutic options the practising dermatologist who treats and follows patients with certain skin disorders is encouraged to screen for HCV infection.

Screening for HCV infection in such a "silent pool" has several advantages. It should identify a large number of infected patients not (yet) presenting with hepatic symptoms but who require long-term surveillance to track disease progression and advice on life-style modification (e.g. alcohol avoidance). It should also identify patients already requiring treatment to prevent terminal, life-threatening complications of chronic hepatitis. Screening for HCV infection in certain dermatological conditions may lead to antiviral treatment being effective in curing cutaneous diseases. Moreover, such an identification will help prevent further transmission of HCV. Hepatitis C is a sexually transmitted disease as well.

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