Lichen planus in hepatitis C virus infection: an early marker that may save lives

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SUMMARY

Hepatitis C virus (HCV) represents a major public health problem as a causative agent in developing chronic hepatitis, cirrhosis, and hepatocellular carcinoma. In recent years it has become known that HCV induces a broad spectrum of extrahepatic manifestations, including some cutaneous ones such as mixed cryoglobulinemia, porphyria cutanea tarda, leukocytoclastic vasculitis, lichen planus (LP), sicca syndrome, and others. Although the association of HCV infection with cryoglobulinemia has been well established, several controversies exist regarding the relationship between HCV infection and LP. This review focuses on the dilemma in evaluating the potential role of LP in diagnosing HCV infection as one of the first overt markers of potentially fatal chronic liver disease.

KEY WORDS

hepatitis C, lichen planus

Introduction

Hepatitis C virus (HCV) has been found to be a principal cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma, as well as the leading indication for liver transplant in Western countries (1). In 1999, the World Health Organization reported that there were 169.7 million cases of HCV infection worldwide, with 31.9 million in Africa, 13.1 million in the Americas, 8.9 million in Europe, 21.3 million in the eastern Mediterranean, 32.3 million in southeast Asia, and 62.2 million in the western Pacific (2). Prevalence rates vary widely, ranging from 0.15% in Scandinavia to 38% in northern Egypt.

Hepatitis C

Infection with HCV is characterized by an extremely high propensity of progression to persistent infection leading to chronic liver disease, which may evolve into cirrhosis and hepatocellular carcinoma in a proportion of patients. Acute infection is usually asymptomatic with persistent, chronic infection developing in 43 to 86% of cases (3). Due to the lack of symptoms and major risk factors, the vast majority of chronically infected individuals remain undiagnosed and unaware of the infection for several years until overt complications secondary to decompensated liver disease eventually develop. In addition, these people may serve as a reservoir of

HCV transmission to others. The natural history of HCV infection varies greatly and is only partially understood. It is characterized by a rather indolent clinical course that can be profoundly influenced by host and virus factors, as well as numerous environmental cofactors (4).

Association between lichen planus and chronic hepatitis C virus infection

Although the liver represents the major site of viral replication, a broad spectrum of extrahepatic manifestations has been suggested as being associated with chronic HCV infection, including mixed cryoglobulinemia and membranoproliferative glomerulonephritis, autoimmune thyroiditis, non-Hodgkin's lymphoma, neuropathy, lymphoproliferative disorders, and some cutaneous manifestations, such as porphyria cutanea tarda, leukocytoclastic vasculitis, lichen planus (LP), sicca syndrome, and others (5, 6). Extrahepatic manifestations are quite common; they were reported in 74% of patients that had at least one clinical extrahepatic manifestation in a large prospective cohort study by the METAVIRC group (7). Some of these may often represent the first overt sign of asymptomatic chronic liver disease. Although the association of HCV infection with cryoglobulinemia has been well established, several controversies exist regarding the relationship between HCV infection and LP.

Lichen planus is a common skin disease with an overall prevalence of 1 to 2% in the general population (8, 9). It is a chronic inflammatory disease presenting a characteristic, usually pruritic papular clinical picture of unknown etiology, affecting the skin and mucosa in various regions of the body. The first report indicating an association between chronic liver diseases and LP was published in 1978 (10). After the identification of the HCV genome in 1989 (11), several studies have reported the coexistence of chronic hepatitis C and LP, particularly oral LP (OLP), with a prevalence of 1 to 4% in the general population (12, 13). Namely, the wide range of factors that may precipitate the cell-mediated reaction resulting in LP lesions also includes viruses (12).

However, the relationship between HCV and LP remains a matter of controversy. Using the keywords *hepatitis* and *lichen planus* in a search of the MEDLINE computerized database, 263 citations from between 1966 and 2003 were found (14). Since the first report on this topic in 1991, more than 80 papers worldwide have suggested an association of LP and HCV, many among them representing controlled studies. Several papers denied any connection between the two entities. The studies varied in terms of populations enrolled, study designs, and the distribution of possible confounders, and revealed several important biases that made firm conclusions impossible.

In March 2003 a consensus meeting was held in France to discuss the most controversial aspects of OLP focus as well on the relationship between OLP and HCV infection based on analysis of the literature (15). By that time, 36 studies had analyzed the prevalence of HCV infection among LP patients. In 20 out of 25 studies, the proportion of HCV-positive persons was higher in the LP group compared to the controls (16). The odds ratio (OR) of the pooled data from all studies showed a statistically significant difference in the proportion of HCV-seropositive persons among LP patients compared to controls. However, the OR for OLP did not change substantially, increasing only in the studies from Mediterranean countries, whereas it halved in studies from northern Europe, becoming insignificant. In studies from countries with the highest HCV seroprevalence (Egypt and Nigeria), there were insignificant or even negative associations (17, 18).

On the other hand, a few studies investigating LP in HCV-seropositive persons showed a prevalence generally higher than expected (from 1.6% to 20%), independent of geographical region (19, 20). These findings may suggest that any LP-HCV association cannot be explained on the basis of high HCV seroprevalence in the general population only. Possible genetic differences among the populations studied (HLA-DR6 allele in Italy), the putative pathogenetic link between LP and HCV with a strong suggestion of HCV-specific T cell response, and several other proposed mechanisms are to be studied thoroughly (15, 21). However, to date there is no firm evidence to answer the question about the connection between the two entities (22).

Potential clinical role of lichen planus in chronic hepatitis C

Nowadays, HCV-related liver disease represents a major public health problem. The overall prevalence of anti-HCV antibodies in the United States is 1.8%, or 3.9 million, based on an analysis of 21,241 serum samples from US citizens over 6 years of age that participated in a large national epidemiological study from 1988 to 1994 (23). Seventy-four percent or 2.7 million of these were actively infected. Another analysis showed that 1.7 million Americans have had hepatitis C for over 20 years and, by 2015, this number will have increased to 3 million (24). With a 12.5% progression rate to cirrhosis over the 20-year course of infection, there are at present 212,500 Americans with hepatitis C and cirrhosis, and the number will increase to 375,000 by 2015. Applying the US rates for the proportion of HCV positivity, the duration of the infection, and the time to de-

velop cirrhosis to the world's population of HCV infected, 7.8 million people currently have cirrhosis and by 2015 there will be 13.8 million cases of cirrhosis due to HCV infection if this is not properly managed (25).

In the last few years, considerable progress has been made in the knowledge of the epidemiology, natural history, and factors influencing the course of HCV infection. Even though it is a viral disease, the most impressive progress has been achieved in the field of efficacy treatment of chronic hepatitis C (26). With a combination of pegylated interferon alpha and nucleoside analogue ribavirin, a sustained virological response has been observed in roughly 50 to 60% of those treated, reaching as much as 93% in some subgroups of patients (27, 28). Still, the most important goal to achieve at present is early diagnosis, in order to potentially improve the survival of patients with chronic hepatitis C. The rate and speed of the disease progression from initially mild to severe and end-stage disease is not a linear process and is influenced by several cofactors including the duration of infection prior to treatment (29). It has been established that early successful treatment of HCV infection prior to overt end-stage disease leads to dramatic improvement of inflammatory liver damage and fibrosis (30). Therefore, every effort should be made to discover infected persons as soon as possible. In this way, proper management of the infection can be offered: either the introduction of relatively successful treatment, or precise and appropriate monitoring to prevent fatal consequences.

From this point of view, evaluating the potential clinical role of LP in diagnosing HCV infection seems to be an extremely practical and pivotal task. The skin and oral cavity are easy to observe. The presence of cutaneous LP and OLP can potentially be used as a marker of HCV infection in asymptomatic patients, leading to proper diagnosis and early treatment and, possibly, a better prognosis of chronic hepatitis C. In addition, identifying extrahepatic manifestations of HCV infection has important implications for these patients' ongoing care. However, if the association is not valid, the routine testing of patients with LP for HCV infection may lead to unnecessary costs and other harmful effects, such as increased anxiety among the people tested. Therefore, it is important to determine whether there is an association between LP and HCV infection so that guidelines regarding routine HCV testing of patients with LP may be introduced to clinicians.

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