Oral lichen planus and hepatitis C virus: is there real association?

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SUMMARY

Lichen planus is an inflammatory, mucocutaneous disease that in addition to the skin involves oral mucosa in about 60-70 % of cases. In recent years, several reports have supposed a relationship between oral lichen planus (OLP) and chronic liver disease, especially hepatitis C (HCV). Here we present an extensive review of the literature in English that examines the association between HCV and OLP.

KEY WORDS

hepatitis C virus infection, oral lichen planus, possible association

Introduction

Lichen planus (LP) is a chronic inflammatory cutaneous disease that frequently involves oral mucosa. It affects 0.5-2.0% of the population with a predilection for women and a mean age of onset in the fourth to fifth decade (1). The hall-mark of cutaneous LP is the presence of itchy, flat-topped, polygonal, glistering papules with a violaceous hue. LP may present in varying forms, and these include linear, annular, atrophic, hypertrophic, vesiculo-bullous, erosive, follicular, and actinic LP.

Oral lichen planus (OLP) develops on the buccal mucosa in about 60-70% of cases. Most of the cutaneous lesions are self-limiting, but the oral lesions are chronic, and rarely undergo spontaneous remission. The oral manifestations of LP have been well described in several large studies comprising patients from dental referral centers and universities around the world (2,3). Six clinical forms of OLP have been described (4) but a simpler clinical classification includes three types of lesions: reticular, papular and plaque as well as atrophic and erosive. Patients with OLP frequently have concomitant manifestations in one or more extra-oral sites. This association was emphasized in a recent study, in which vulva and vagina were involved in approximately 25% of cases. Lesions involving the scalp, nails, esophagus or eyes occur less frequently (5).

Etiology and pathogenesis of LP

The etiology and pathogenesis of LP remains unclear. Some immunological and hereditary factors been

suggested. Hepatitis C virus (HCV) infection and chronic liver conditions have also been suggested (6). The possible association between LP and HCV infection is still controversial. Many reports have mentioned such an association (7,8,9). The possible etiopathogenic mechanism that links the two diseases remains unclear (10). In addition to a possible common etiopathogenic factor which has not yet been established, various researchers have suggested that the simultaneous appearance could be due to genetic, environmental, geographic, or other factors (10,11). In OLP, HCV replication has been reported in the oral mucosa of anti HCV/HCV-RNA positive patients. In fact, some studies showed that both the plus and minus strands of viral RNA are detectable in epithelial cells from normal oral mucosa and from the LP lesions by reverse transcription/polymerase chain reaction or in-situ hybridization (12). As a replicative form of HCV-RNA can be detected within OLP lesions and an immune-mediated damage of basal layer cells, is always present in these patients, evidence for a link between the cell mediated immune response against HCV and the pathogenesis of OLP has recently been reassessed by Pilli et al (13). They have shown a HCV-specific T-cell responses at the site of OLP lesions, sustained by terminally differentiated effector cells, strongly suggesting their role in the pathogenesis of tissue damage.

Hepatitis C virus

The hepatitis C virus is an RNA virus and is a major cause of acute and chronic hepatitis. It is contracted chiefly through parenteral exposure to infectious material such as blood transfusions or infection with dirty needles. At high risk from HCV injection are drug users sharing needles, and health care workers. Chronic hepatitis C develops in about 75% of those infected. Both acute and chronic hepatitis C are asymptomatic in most patients. However, chronic hepatitis C is a slowly progressive disease and results in severe morbidity in 20-30% of infected persons. It is associated with a host of extra hepatic manifestations, many of which may be seen by dermatologists (14).

Pathogenesis of the association

Although the manner in which the HCV infection predisposes patients to the development of LP remains unclear, some speculate that long-term infection may lead to an aberrant immunologic response. While it has been suggested that LP may be triggered by HCV, no clear evidence of viral infection has been found at the site of cutaneous involvement (15). Other studies (16,17) support the current view that host immune response rather than the viral factors is of greater importance in the development of OLP lesions in HCV infected patients. The role of environmental or geographical factors, however, is less clear. It has been suggested that geographic localization could explain the different association between HCV and OLP. A higher frequency of HCV infections in certain countries would increase the chance that a patient with OLP would also be infected with HCV (11). Mega et al (18) noted three types of OLP: OLP associated with a HCV infection (OLP-HCV), oral lichen-contact sensitivity reaction (OLCSR) and idiopathic oral lichen planus (IOLP), all of which exhibited a similar histopathology. However, some OLP-HCV cases showed deeper lymphocyte infiltration in the lamina propria than in IOLP, and more extensive and aggressive lymphocyte infiltration could be associated with the erosive manifestation of OLP-HCV. Immunohistochemically, a similar distribution of the CD4 cells was observed in all the OLP groups. In all OLCSR cases, moderate to intense CD4+ cell infiltration was seen in the connective_tissue papillae and the CD4+cell proportion was higher than in IOLP. In contrast to the CD4+ cell, a significantly different distribution of CD8+ cells was observed in OLP-HCV and OLCSR. The CD8+ cell proportion of OLP-HCV in lamina propria was significantly higher than in IOLP, while the CD8+ cell proportion of OLCSR in both the epithelium and connective tissue papillae were significantly lower than in IOLP. Although the pathogenesis of OLP-HCV remains to be elucidated, some reports have supported a host factor caused by HCV infection rather than a reaction to local HCV as an exogenous antigen. On serological examination, significantly increased several levels of the soluble intercellular adhesion molecule (ICAM)-1 and IgG in OLP-HCV patients, suggest the implication of host factors. Further more, HCV replication has been reported in the epithelial cell of oral mucosa from HCV patients with and without OLP, using both RT PCR (19), and in-situ hybridization (12). HCV as well as other factors seem to be responsible for OLP-HCV. In the lamina propria of OLP-HCV, the different function of the CD8+ cells with different functions, cytotoxic and suppressor, have been reported in vitro (20). Further examination of the CD8+cells in each tissue component of OLP-HCV is needed to evaluate the different distribution of CD8+ cells (18). Langerhans cells, which play a key role in the presentation of antigen in OLP have been reported as either increased in number or activated in OLP, showing the expression of S-100, HLA-DR and CD1 (21,22). Mega and his co-workers (18) could not confirm that a significant increase of S-100+ cells was characteristic of all OLP-HCV cases.

Lazaro et al (23) have demonstrated that HCV infects keratinocytes from cutaneous LP lesions and that the viral RNA is translated in these cells as demonstrated by the HCV incorporated in the skin biopsies. Klanrit et al (24) showed a small but significant percentage of

HCV infected patients with OLP. The study of Harman et al (15) supported the view that the consistency of HCV and LP is probably more than coincidental and they recommend that it is appropriate to screen all patients with LP for HCV infection.

Prevalence of the association

In recent years, several authors have reported a relationship between OLP and chronic liver disease, especially hepatitis C. This association seems to be strong in Japanese and Mediterranean populations, probably due to the higher prevalence of HCV infections. Mignogna et al (9) found that 28.8 % of OLP patients were HCV positive with a statistically significant difference compared to a control group. In another study (1), they classified OLP into OLP-HCV+ and OLP-HCV– patients in order to assess possible differences in the clinical features between the two groups of patients. This important variability suggests that HCV may play a role in the development of OLP, probably through modulation of qualitative aspects of the inflammatory infiltrate. They found a statistically significant difference between OLP-HCV-and OLP-HCV+ patients.

Other studies, however, failed to show a significant association between LP and liver disease, or to detect any serological abnormalities of liver disease in oral lichen planus (OLP) patients. The geographic variation in the prevalence pattern of HCV infection could account for this contradictory data (11).

The prevalence of HCV infection in patients with LP varies considerably from one geographic area to another, ranging from 4 % in northern France to 62 % in Japan. On the other hand, studies from Great Britain have failed to reveal any association. In a report from Germany, 2.4 % of 127 HCV-positive patients had OLP, but only 1 of 24 consecutive patients with LP was anti-HCV seropositive (14).

Well-controlled studies have demonstrated a strong association between chronic liver disease and/or hepatitis C (HCV) infection and OLP. Several investigators have even suggested that HCV could be directly involved in the development of OLP since HCV viral sequences were found in sera of patients with OLP and in oral tissue samples. Elevated liver function tests had been detected most often in patients with erosive diseases and appear to correlate with the severity of OLP.

Many other studies reported a high prevalence of HCV infection in patients with LP. The prevalence of anti-HCV anti bodies in patients with cutaneous lichen planus (CLP) and for oral lichen planus (OLP) ranged from 3.8 % to 65 % (8,25). Imhof et al (26) found, in a controlled study, a significant association between LP and HCV, while Grote et al (27) did apparently not find any association in an uncontrolled study. In the USA a significant association between LP and HCV infection was reported in all but one study (28). Recently, a report from Brazil suggested an association between OLP and HCV (11), while reports from Nepal (29) and Nigeria (30) noted no such association. Interestingly, the report from Nigeria found that the prevalence of HCV in LP patients was higher than in normal controls and not necessarily in LP as a specific entity but also in other dermatomes reportedly associated with HCV (5).

The association of HCV infection and LP has been investigated in the Ankara and Gazian Tep regions of Turkey. In the controlled study from Ankara, any association of HCV infection with LP was excluded. However, 6.84% of LP patients detected positive for anti-HCV antibodies (31,32).

In a study by Rahnama et al (33) from Iran for detection of HCV antibodies in patients with LP, it was found that one out of 66 patients and three of the controls were antibody positive and there was no statistically significant difference between the two groups.

Conclusion

There seems to be an association between the OLP and HCV infection. The association of OLP with both HCV infection and liver disease appears to be dependent on geographic factors and more so given the erosive presentation of OLP. In our opinion, different results may be due to the variation of the incidence of HCV infection in different countries. Serology for HCV and liver enzymes should be made in any suspected lesions of OLP, especially those with erosive form and in areas where the prevalence of HCV infection is high, before proceeding to a skin biopsy. This very important step is necessary to prevent the incidental transmission of HCV to health workers and to prevent the transmission of HCV through infectious material. Further studies are recommended to prove the current hypothesis regarding the association and pathogenesis of the association between LP and chronic liver disease and/or HCV infection.

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