Review Article

Oral Conditions Associated with Hepatitis C Virus Infection

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ABSTRACT

Hepatitis C virus (HCV) infection in more than 170 million chronically infected patients with no developed preventive vaccine is a globally important issue. In addition to expected hepatic manifestations, a number of extrahepatic manifestations, such as mixed cryoglobulinemia, glomerulonephritis, polyarteritis nodosa, rashes, renal disease, neuropathy, and lymphoma, have been reported following HCV infection, which are believed to be influenced by the virus or the host immune response. HCV combination therapy with pegylated interferon and ribavirin might be associated with side effects as well. The association of HCV with special oral conditions has also been reported recurrently; the mechanism of most of which remains unclear. This article reviews the association of HCV infection with some of the oral conditions such as oral health, Sjogren's syndrome, lichen planus and oral cancer.

Key words: Hepatitis C, lichen planus, oral cancer, oral diseases, oral health, salivary gland, Sjogren's syndrome

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Hepatitis C virus (HCV), known previously as parenterally transmitted or posttransfusion non-A non-B hepatitis, was first identified and cloned in 1989. It is an enveloped, single-stranded positive-sense RNA virus, having a diameter of about 50 nm and classified as a separate genus (*Hepacivirus*) within the Flaviviridae family.[1,2]

After two decades, with more than 170 million chronically infected people worldwide (3% of the world's population), HCV is now considered as a disease of significant global importance. Although HCV incidence is lower than that of hepatitis B virus (HBV) in many parts of the world, the rate of its chronic infection is much higher[3] and its mortality rate is increasing.[4-6]

Six major genotypes (1-6) of HCV with various geographical distributions have been identified until now.[1,7]

The routes of transmission are intravenous drug use, nonprotected sexual contact with multiple partners, iatrogenic acquisition (e.g., hemodialysis), accidental exposure such as needlestick injuries, and less frequently vertical transmission from mother to child. However, no obvious route of acquisition can be identified in 30-40% of HCV infections.[8,9]

The combination therapy with pegylated interferon and ribavirin, focused on achieving a sustained virological response (SVR), is usually accompanied with side effects.[10-12]

The morbidity from HCV infection is not only a result of the sequelae of cirrhosis, but also to approximately 30 reported extrahepatic manifestations (EHM), such as

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mixed cryoglobulinemia, glomerulonephritis, polyarteritis nodosa, rashes, renal disease, neuropathy and lymphoma as well. Despite the available reports, association of some of the other disorders with long-term HCV infection remains controversial.[13-17]

It is believed that HCV EHMs are influenced by the virus itself or the host immune response following HCV infection, the mechanism of most of which remains unclear.[18,19] The association between HCV infection and some of the oral conditions (oral health, Sjogren's syndrome, lichen planus, and oral cancer) are reviewed in the present article.

ORAL HEALTH

Anecdotal evidence strongly indicates that HCV-infected patients are prone to tooth decay; suffer from esteem loss due to poor oral aesthetics; and have difficulty having a healthy diet due to their poor oral health, being attributed to the number of factors such as injecting drug abuse, methadone medication, and poor utilization of dental services.[20,21] Chronic diseases are believed to increase the risk of developing dental and oral diseases derived from biological mechanisms either directly (e.g. probable increased risk of developing periodontal disease associated with a diabetes-induced inflammatory response) or indirectly (probable increased risk of dental caries in HCV-infected patients by decreased salivary flow due to prescribed medications).[22,23]

The provision of dental care falls outside the mainstream of medical funding and the costs of dental treatment are often prohibitive. In addition, HCV infected patients, admitted to the government dental clinics, are often placed on extremely long waiting lists. The inaccessibility of dental treatment may also contribute to the reported extensive tooth destruction and subsequent poor oral health.[20,24]

The results of a study in the United States showed that high levels of dental treatment are needed among HCV-infected patients.[22] Additionally, a marked discrepancy was shown between the oral health of the HCV infected group and the control in another study in Australia. Both groups were eligible for public dental care, confronting similar access problems and difficulties with waiting lists. However the experience of infected subjects was significantly more worse than HCV-noninfected ones. The number of missing teeth was also significantly higher in HCV-infected patients and periodontal health tended to be poorer.[20]

According to the limited data about the oral health status of HCV-infected patients, mainly from the developed countries, oral health treatment seems necessary. More studies should be performed in the developing countries to make better evaluation of the oral health of HCV-infected patients; where equipment is limited and disorder is more prevalent.

Previous reports have also revealed that some dentists prefer not to work on patients with bloodborne infections,[25-28] highlighting the continued need for educational courses for dentists to change their attitude and behavior toward infected patients. In addition, routine dental examination of infected patients is recommended to prevent common dental and oral disorders within this group.

SJOGREN'S SYNDROME AND SALIVARY GLAND CONDITIONS

The first description of Sjogren's syndrome (SS) was by Mikulicz in 1892, who described a 42-year-old man with bilateral enlargement of the parotid and lacrimal glands associated with a small-round-cell infiltrate.[29]

SS is a chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates in the affected glands. Dryness of the mouth and eyes results from the involvement of the salivary and lacrimal glands.[29-31] The exact etiology of SS is unknown. Besides other possible factors, a viral etiology has been suggested.[32,33] However, no single infective causative agent has been identified until now.[34]

Several reports have initially suggested an association between HCV and SS following the development of serological tests,[14,15] which has been supported with more than 250 reported cases of SS–HCV.[35] Garcia-Carrasco *et al*. reported an HCV prevalence of 14% among the patients with a previously identified primary SS, which was significantly higher than that of the general population (1.2%).[36] The occurrence of a typical autoimmune sialadenitis in HCV-positive patients, similar to that explained in primary SS, suggests that HCV might efficiently be involved in the SS pathogenesis.[35] Up to 75% of HCV-infected individuals have histological evidence or a test abnormality (ie, xerophthalmia detected by Rose Bengal stain, Schirmer test, sialometry) consistent with SS.[18] Up to 80% of HCV-infected individuals may have some salivary or lachrymal abnormalities, frequently represented by histological signs of mild sialadenitis, whereas clinical evidence of dry mouth and dry eyes is often absent (or may be underestimated).[37]

Proposed mechanisms for such a correlation include cross-reactivity between the HCV envelope and host salivary tissue or HCV envelope-mediated immune stimulation against salivary glands. These mechanisms are supported by studies in mice that were transgenic for the HCV E2 envelope protein.[18]

Distinct differences have been reported between HCV-associated SS and primary SS, namely the absence

of anti-Ro/SS-A and anti-La/SS-B, ribonucleoprotein, Jo-1, proliferating cell nuclear antigen, or Scl-70.[17,38] Several studies have assessed the morphologic and immunohistochemical characteristics of sialadenitis in HCV patients. These results indicated that HCV patients had patterns of salivary gland disease similar to those seen in primary SS patients.[39-41] SS and HCV infection have similar pathogenic characteristics. These derangements include overproduction of autoantibodies as a result of B-lymphocyte hyperactivity and expansion of CD5+ B cells that are involved in the production of polyreactive autoantibodies and rheumatoid factor. In addition, analysis of three HCV-infected patients demonstrated a predominance of B cells over T cells in the lymphocytic focus and an increased expression of T lymphocytes in the inflammatory infiltrate.[35,42]

Approximately 12% of all HCV-infected patients receiving Peginterferon/ribavirin therapy develop xerostomia, which in turn increases the risk of symptoms such as dental cavities, nausea, and constipation. A recent Italian study demonstrated that dry mouth occurring during anti-HCV therapy results from a reversible inhibition of salivary gland function that does not appear to be dose dependent and is promptly reversed upon cessation of treatment.[43]

Different mechanisms may participate in the pathogenesis of SS associated with HCV infection. These happen via direct infection and proliferation of HCV in salivary glands, molecular mimicry between HCV and salivary glands, and formation of immune complexes containing HCV.[35,44] It has also been demonstrated that replication of the virus itself in the salivary gland epithelial cells might result in hyposalivation.[5]

The pathogenic role of HCV infection in SS remains an issue of debate. Part of this may be a result of misdiagnosis or misclassification and due to the lack of well-defined and commonly accepted diagnostic criteria. The San Diego criteria require objective evidence of sicca syndrome plus evidence of systemic autoimmune disease (eg., autoantibodies and a characteristic minor salivary gland histopathology appearance). At the other end of the spectrum, the European criteria do not require the presence of autoantibodies or a positive salivary gland biopsy finding. Thus, the number of patients fulfilling the European criteria is fivefold to tenfold greater than those fulfilling the San Diego criteria. It has been proposed that HCV infection is a criterion to rule out a primary diagnosis of SS, especially if cryoglobulinemia and hypocomplementemia are present and anti-SSA/Ro antibodies are absent.[37,45,46]

LICHEN PLANUS

Lichen planus (LP) is a common T-cell-mediated chronic inflammatory disease of the stratified squamous epithelium with unknown etiology. It can affect the oral mucosa, skin, genitalia, hair follicles, nails, esophagus, urinary tract, nasal mucosa, larynx, and even eyes.[19,47,48] Clinically, the oral lichen planus (OLP) has six variants: Papular, reticular, plaque-like, atrophic, erosive, and bullous. These features may occur individually or in combination.[49] Oral manifestations of LP may occur in the absence of skin lesions. The erosive form of OLP causes extreme discomfort and may also be premalignant.[15,50]

The association of LP with viral agents has been of researchers' interest for a while. Accordingly, one of the most frequently reported oral EHM of HCV infection is OLP.[46,51] The association between HCV and LP was first described in 1990, a year after the discovery of the virus itself.[52] The investigations were all on antibody-based serological examination. Therefore, the probable association between HCV infection and OLP could not be proved initially.[15]

Although the prevalence of LP among HCV-infected patients has been estimated to be about 5%, the prevalence of anti-HCV in LP patients has been estimated to be as high as 38%. A recent study of 1557 LP patients showed a higher HCV prevalence compared with the control group (1.9% and 0.4%, respectively, $P < 0.001$). Additionally, a multivariate analysis indicated that LP was associated with HCV infection (OR 4.19, 95% CI 2.21; 7.93).[53]

Indeed, based on the geographical association of HCV and LP, the prevalence of HCV infection among OLP patients varies widely between countries, reaching the highest percentage in HCV hyperendemic areas.[54] Accordingly, the results of a recent systematic review and meta-analysis showed that LP may be significantly associated with HCV infection mainly in Mediterranean countries, Japan, and the United States. Such a possible association has been strongly and consistently suggested through other subanalyses and the sensitivity assessments performed on the issue as well. Because HCV can replicate in skin and oral mucosa, and also since HCV-specific T cells have been found in OLP specimens, the virus could be involved in the pathogenesis of a number of OLP cases, probably via an immunological pathway that are still to be defined.[13] Analysis of experimental data strongly suggests that HCV is involved in the pathogenesis of OLP via local induction of an immune response specific for HCV epitopes.[37]

The role of particular HCV genotypes in the pathogenesis of HCV-related OLP is unlikely, given the observation of LP association worldwide with the same genotypes commonly

found in patients without LP. However, genotype 1b seems to be associated with LP, and it appears to be uncommon in the United Kingdom. Studies have shown no differences in serum levels or HCV-RNA levels between HCV-infected patients with and without LP.[37]

Some studies have shown that interferon and ribavirin treatment can improve OLP in HCV-infected patients.[16,38,55] Other studies have shown that OLP may develop or worsen after HCV antiviral treatments.[56] Therefore, the use of interferon in patients with HCV and LP should be undertaken with great caution.[17]

HCV-associated hepatic disease may precede LP onset or may be diagnosed together with it. Apparently, there are no significant differences in the histopathological characteristics specific to OLP or in the ratio of T cells and B cells among infiltrating lymphocytes regardless of the presence or absence of HCV infection.[37,56,57] However, the proportion of CD8+ T cells in the lamina propria appears to be higher in HCV-related OLP compared with idiopathic OLP.[34]

Recently, a different genetic cytokine background has been reported in OLP patients with and without HCV infection. Indeed, in the idiopathic form of OLP, the increased production of tumor necrosis factor alpha and interferon gamma is the result of genetic dysregulation of the immune response,[33,37] whereas OLP patients with HCV infection have a Th1 cytokine bias, possibly secondary to an abnormal immune response to the virus.[34]

With regard to previous studies on the association of OLP and HCV, it is possible to identify some analytical inconsistencies: (1) control groups identified without analyzing the age-specific prevalence of anti-HCV positivity; and (2) inadequacy of previous data toward the real prevalence of HCV infection in the general population.[58]

Hence, it seems too soon to reach a definite conclusion. During recent years and following the development of immunoassays for the detection of anti-HCV antibody, there has been a substantial amount of work on the subject, results of which varied widely, ranging from a strong association to a lack of association.

HCV-RNA has been detected both in sera and in oral lesions of patients with OLP; however, no direct pathogenic effect of HCV on the oral mucosa could be demonstrated. Theoretically, epitopic similarities between HCV and keratinocytes could explain the association between LP and HCV, but this could not be demonstrated in any studies. It is believed that this association might be related to the cytotoxic immune responses to the epithelia cells infected with HCV.[32]

However, when HCV infection is present with OLP, some additional factors, which remain unknown, must also be present. Thus, HCV may be a contributory cause but it is neither necessary nor sufficient to cause OLP on its own. Further studies are required to identify the relevant cofactor (s).[15] It is still highly controversial whether OLP can be considered as an extrahepatic manifestation of HCV infection. Clinicians must always keep in mind that OLP may be associated with a systemic disease.[19] Well-designed prospective, especially cohort studies, mainly from countries with low prevalence of HCV infection, are clearly needed.

ORAL CANCER

Oral cancer is a major public health problem in many parts of the globe. It accounts for approximately 400,000 new cases of diagnosed cancers annually. Additionally, it is the cause of 200,000 deaths per annum. Epidemiologic studies revealed a wide range of oral cancer prevalence in different parts of the world, the majority of which confirmed an increasing rate, morbidity, and mortality in the past years.[59,60] Oral squamous cell carcinoma (OSCC) is the most serious and most common oral malignancy accounting for almost 95% of all lesions.[61]

Although there is no evidence to confirm oral cancer as an HCV EHM, there are studies showing that HCV is very likely to be involved in the development of oral cancer.[62,63] Several studies have been carried out during recent years to better understand the role of HCV in the development of oral cancer and precancerous lesions.[64,65]

The incidence of HCV infection in Japanese OSCC patients has been reported to be 16.7-24%. They also investigated the prevalence of HCV infection in oral cancer patients with multiple primary cancers (MPCs) as a risk factor in patients with OSCC. Of 327 patients with OSCC, 59 (18.0%) showed MPCs. In the OSCC patients with MPCs, serum HCV antibodies (anti-HCV) and HCV-RNA were detected in more than 36% and 28%, respectively.[66,67] The same group of investigators reported a patient with chronic hepatitis C, who developed oral cancer. They also detected HCV-RNA in the oral cancer tissues.[62] In a study on the prevalence of hepatitis virus infection in association with oral diseases requiring surgery performed in Japan, Takata *et al.*, found that HCV antibody was higher in patients with oral cancer. However, the authors concluded that increased incidence of HCV antibody apparently was a reflection of age and that HCV infection may not have an etiologically important association with oral cancer.[68]

On the other hand, an uncontrolled study in the United States reported that 21% of 99 patients with head and neck SCC had HCV infection.[69] Other studies also demonstrated

that potentially oral premalignant lesions, such as leukoplakia and oral epithelial dysplasia, are not associated with HCV infection.[70-72]

In a retrospective study on 402 OLP patients, the role of HCV infection on OLP outcome was analyzed.[73] Although 44% of the patients who developed an oral cancer were HCV infected, the risk was not significantly increased, possibly because of the low statistical power. However, HCV is a common cause of liver cirrhosis, which may present itself as an independent risk factor for the development of oral cancer.[34,74]

It is very important to detect the lesions in patients with oral cancer when they are at a primary stage. All these findings emphasize the importance of periodic examination of the oral cavity among patients with HCV infection. Studies on the role of immunological pathways as well as the mechanism of the development of the disease are recommended.

CONCLUSION

Based on the published findings, OLP and SS may be significantly associated with HCV infection, and the virus may be involved in the pathogenesis of these diseases, probably via an immunological pathway. OLP association with HCV was found to be influenced by a geographical distribution. The association of other oral conditions with HCV infection, however, needs further investigation. The association between certain chronic diseases and an increased prevalence of dental disease suggests that many systemic diseases have oral manifestations. Thus, dental professionals could be an important resource for screening and referring patients with chronic diseases. A fast, accurate, and relatively inexpensive oral test has been used to diagnose HIV, and a new oral test should be available soon for HCV.

It should also be emphasized that the therapy options of the above-mentioned oral conditions in the presence of HCV infection has been considered the same as noninfected patients in the related manuscripts. Other probable therapy suggestions should be evaluated in case–control studies to clarify this issue.

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