

Potential pathogenic mechanisms involved in the association between lichen planus and hepatitis C virus infection (Review)

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Abstract. Lichen planus (LP) is an immune-mediated inflammatory disease that particularly affects the skin and mucous membranes. Its etiology remains elusive, however some trigger factors, including viral or bacterial antigens, drugs and metals, have been postulated. There is a higher prevalence of hepatitis C virus (HCV) infection among patients with LP, with some geographical variations. HCV is an enveloped RNA virus that belongs to the Flaviviridae family and in most instances causes chronic liver infections. It has been hypothesized that HCV may contribute to LP development, but the link between the two disorders is not fully understood. It is still debatable whether HCV leads to the occurrence of LP lesions directly by replication inside the infected cells or indirectly by activating immunological pathways. Molecular studies have revealed HCV RNA in specimens collected from patients with LP. The auto-immune theory was also suggested given that several studies have revealed viral replication and immune response activation associated with autoantibody synthesis. The aim of this review is to summarize the main potential mechanisms involved in the association between LP and HCV infection. Understanding the link between the two disorders may shed some light on the pathogenesis of LP, which is a challenging issue.

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1. Introduction

Globally, there are 120-130 million individuals infected with hepatitis C virus (HCV) and 3-4 million new cases are identified each year (1). The main risk factors for getting the infection are the use of injectable drugs, the contact with contaminated instruments and blood transfusions from unscreened subjects (2). HCV, first described in 1989, is a single stranded RNA virus, that belongs to the Flaviviridae family. HCV is a significant cause of liver cirrhosis and hepatocellular carcinoma (3,4). To date, seven genotypes have been described and their prevalence present certain geographical variations. The pathogenesis of the infection involves the activation of cytotoxic T lymphocytes which during the fight against the virus lyse the infected hepatocytes and produce liver damage (5).

Mokni *et al* were the first to note the association between HCV and lichen planus (LP) in 1991. They reported a case of a patient who presented with an eruption consisting of violaceous papules disseminated on his arms and trunk. Laboratory findings showed elevated transaminases and further tests confirmed the diagnosis of HCV infection. A cutaneous biopsy established the diagnosis of LP (6). Three years later, the first cases of oral lichen planus (OLP) in association with HCV

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infection were notified. These studies were published shortly after the isolation of HCV in 1989 (7).

LP is a chronic T cell-mediated dermatosis of unknown etiology, which affects the skin, mucous membranes, hair and nails (8). One of the main histopathological features of LP is the vacuolar degeneration of the keratinocytes in the basal layer. This phenomenon is the result of the action of T helper lymphocytes, T cytotoxic lymphocytes, natural killer cells and dendritic cells that predominate in the inflammatory infiltrate. Thus, the main pathogenic mechanisms are increased apoptosis of keratinocytes and the inhibition of apoptosis of T lymphocytes (9-11). The trigger factors remain unknown. LP is associated with certain pathological conditions such as autoimmune diseases, malignancies, stress and viral infections, of which the most notable is HCV infection (9,12).

In the following sections we present the main studies regarding the relationship between LP and HCV.

2. HCV infection and cutaneous manifestations

Numerous studies have shown that a great number of patients with chronic hepatitis C (40-75%) present extrahepatic manifestations (13). Cacoub *et al* conducted a study on 1,614 patients with chronic HCV infection and observed that 74% of them had at least one extrahepatic manifestation, arthralgia, paraesthesia and myalgia being the most common symptoms. Pruritus was identified in 15% of cases and LP in 1%. They found that the main risk factors associated with extrahepatic manifestations are female gender, old age and severe hepatic fibrosis (14). Cutaneous manifestations are present in up to 17% of HCV positive patients. There is important evidence that HCV infection is associated with cryoglobulinemia, LP and porphyria cutanea tarda (15).

The mechanisms involved in the development of cutaneous manifestations in patients with HCV infection are controversial. Viral particles have been identified in various cells (keratinocytes, lymphocytes), a finding which raised the hypothesis that HCV exerts a direct cytopathic effect. Another theory advocates that the virus acts at the level of different organs, and skin manifestations are actually the result of the functional impairment of those organs (16). The theory of autoimmunity is also considered. This theory is supported by the detection of many circulating autoantibodies in HCV patients and the tropism of the virus for lymphocytes that promotes the proliferation of B cells (17).

3. Epidemiological data

The link between LP and HCV is supported by several epidemiological studies which investigated the prevalence of HCV infection among LP patients (18-24). The recent meta-analysis by Lodi *et al* revealed that on average 22.3% of LP patients had anti-HCV antibodies with significant variability depending on the geographic region, data being obtained from the analysis of 70 studies on 6,378 patients. The highest incidence of HCV infection among LP patients was recorded in Japan and Europe, the Mediterranean region (25). Similar results were revealed in the meta-analysis by Shengyuan *et al* (26).

The meta-analysis by Petti *et al*, which focused on the link between OLP and HCV, highlighted that the association

globally occurs in 2% of OLP cases, suggesting that testing patients with OLP for HCV infection should only be performed in countries with an increased number of cases of HCV infection. They draw attention to the fact that the relationship between HCV infection and OLP is dependent on the prevalence of the infection in the analyzed population (27). This observation is also confirmed by the meta-analysis by Alaizari *et al* that revealed geographical differences, for example in France only 4% of subjects with OLP had HCV infection, compared to Italy where the incidence was ~30% and Japan 62%. Alaizari pointed out a 6-fold higher risk of HCV infection among OLP patients (28).

Genetic factors may be responsible for the geographical differences (29). A study conducted in Italy, which investigated genetic aspects, revealed that HLA DR6 alleles are more common in patients with OLP and HCV infection, compared to those without HCV infection. It has been concluded that this finding could provide an explanation for the geographical variability of the association between LP and HCV and suggested that a molecular mimicry between regions of HLA DR6 allele and HCV components may be involved or the presentation of certain HCV encoded peptides by HLA DR6 to T lymphocytes might result in the development of lichenoid reactions (30).

If a specific genotype is involved, it is still a debatable topic. In their study, Lodi *et al* included 39 LP patients infected with HCV; the genotyping was performed in 33 patients with detectable viremia. The prevalent genotype was 1b in 51% of patients (17 cases), followed by 2a (9 cases), 1a (2 cases) and 2b (1 case); in 4 cases the result was indeterminate (31). In the study by Imhof *et al* genotype 1b was also most commonly identified (83% of the patients) (18). Femiano and Scully raised the hypothesis that the HCV genotype might influence the clinical aspect of LP (32).

Another approach of the link between LP and HCV infection is to investigate the prevalence of OLP in HCV infected patients, but such studies are fewer. Henderson *et al* analyzed the oral disorders among HCV patients (40 patients) and identified an increased prevalence of OLP (20%), but the diagnosis of OLP was not confirmed by histopathological examination. Moreover, the study revealed that HCV patients suffer more frequently from oral conditions such as caries, gingivitis and dryness (33). In addition, Grossmann *et al* analyzed the prevalence of oral mucosal lesions and variations in normal aspect of oral mucosa in patients with chronic hepatitis C and found that over 90% of them had changes of the oral mucosa. The most common were Fordyce's spots (44.7%), followed by lingual varicosities (31.2%). However, OLP was the only associated disorder with statistical significance (34).

Conversely, there are studies which did not reveal an association between LP and HCV infection. The study by Stojanovic *et al* on 173 LP patients from Slovenia revealed that only 1.2% of them had anti-HCV antibodies, with no link between the two diseases (35). Another study, conducted in China, also found no association between LP and HCV, anti-HCV antibodies being detected in only 0.7% of patients (36). Other studies have also showed the lack of association between LP and hepatitis C (37-39).

Ali and Suresh conducted a study that included 40 patients with OLP. They identified a strong positive correlation between the level of transaminases and erosive OLP. The link between

HCV infection and OLP could not be evaluated, anti-HCV antibodies being negative in all patients. In medical literature, the incidence of liver disease in patients with LP varies between 0.1-35% (40). In addition, Bombeccari *et al* observed a positive correlation between elevated levels of transaminases and LP exacerbation in HCV positive patients. They recommended the periodic evaluation of transaminases among LP patients with liver diseases, considering that the elevation of aspartate transaminase (AST) and alanine transaminase (ALT) may be an indicator of LP evolution (41).

4. Clinical and histopathological aspects

Several studies focused on the evaluation of clinical and histopathological differences between LP patients with and without HCV infection. It has been noted that OLP patients with HCV infection have more severe and extensive forms. In these patients the OLP evolution is chronic and the response to classical treatments is reduced, with a poor prognosis. It seems that there is a correlation between the severity of liver disease and the exacerbation of OLP lesions (15).

Gimenez Garcia and Pérez-Castrillón conducted a study on 101 patients with cutaneous and/or oral LP and obtained a statistically significant correlation between OLP and HCV infection only in the case of erosive OLP (42). In other studies, the erosive form was also the most frequently diagnosed (15,43). In addition, erosive OLP appears to be more common in patients with LP and liver diseases (42). However, the study by Mignogna *et al* showed that the reticular type was more common in HCV-positive compared to HCV-negative patients (25 vs. 18.7%), and plaque lesions were more common in those without HCV infection. The erosive type was found in equal proportions in the two groups (44). Romero *et al* analyzed 7 patients with OLP and anti-HCV antibodies and 55 patients with OLP without anti-HCV antibodies. In the case of HCV positive patients, lesions on lips, tongue and gums were more frequently observed. In both groups the reticular type was the most common, but the number of lesions was higher in the HCV positive ones (45).

No histopathological differences of LP lesions were observed in HCV positive patients compared to HCV negative patients (46). Mega *et al* analyzed histological and immunohistochemical aspects of samples taken from OLP patients with HCV infection, patients with idiopathic OLP and patients with oral lichenoid reactions and observed similar histological features. However, a higher amount of CD8 lymphocytes was found in the lamina propria in patients with OLP and HCV infection and a lower amount in patients with oral lichenoid reactions compared to idiopathic OLP. Regarding CD4 lymphocytes, there were no differences between the three studied groups (47). Some authors did not detect differences in the proportion of T and B lymphocytes in the inflammatory infiltrate (48).

5. Mechanisms involved in the link between LP and HCV infection

Although in many studies the association between LP and HCV has been observed, the deep mechanisms involved have not been clearly elucidated. Several theories bring various

factors to our attention that may contribute to the development of LP lesions.

Viral replication in keratinocytes. Although, hepatocytes represent the main site where HCV replicates, viral replication was also found in other tissues (49). Some investigators have identified viral RNA in the skin and oral mucosa, with a higher rate in oral tissue (49-52).

Lazaro *et al* included in their study patients with chronic hepatitis C without LP (group 1), patients with LP and chronic hepatitis C (group 2), and patients with LP without hepatitis C (group 3). Biopsies were taken from all patients. Viral RNA was detected in keratinocytes in 69% of group 1 patients, in all group 2 patients and was not identified in group 3 patients (53). Nagao *et al* also identified viral replication in OLP lesions, suggesting its role in pathology (54). The study by Arrieta *et al*, which included 23 patients with OLP, 14 of them having anti-HCV antibodies, and 5 patients with chronic hepatitis C without OLP, revealed viral replication in epithelial cells in all HCV positive patients, irrespective of the presence of OLP (a prior biopsy from the oral mucosa was performed) (55). Since HCV was also identified in the normal mucosa, it has been suggested that the virus has no direct effect on keratinocytes (50).

In contrast, the study by Harden *et al* on a small group of patients did not detect viral RNA in LP samples taken from patients with chronic hepatitis C and did not reveal any improvement of the skin lesions following HCV specific therapy (56). Femiano and Scully did not identify HCV RNA in the oral mucosa samples from patients with OLP and HCV infection, but they detected HCV RNA in peripheral blood lymphocytes (32).

Figueiredo *et al* suggested that the factor involved in the occurrence of OLP lesions is primarily related to the host peculiarities, the host immune response playing a more important role than viral factors (57).

The autoimmune theory. The theory that advocates the presence of an autoimmune process is supported by the identification of autoantibodies in the serum of patients with LP and HCV infection. In addition, in these patients, autoimmune diseases such as autoimmune thyroiditis, and CREST syndrome are often diagnosed (56).

Lodi *et al* revealed circulating antibodies against epithelial antigens in patients with HCV infection and LP but without showing their role in pathogenesis (58). The study by Łapiński *et al*, including patients with chronic HCV infection (25 of them were immunosuppressed), found autoantibodies in the serum of 32.5% immunocompetent and 16% immunosuppressed subjects. Antinuclear antibodies have been most commonly identified (59). However, Carrozzo *et al* revealed that patients with LP infected with HCV do not have higher titers of autoantibodies than those HCV negative. Higher levels of serum immunoglobulins were identified; this can be explained by the presence of cryoglobulins in these patients (60).

It is thought that HCV induces alterations of antigenic structures of oral mucosa resulting in the activation of cytotoxic T lymphocytes or the initiation of a humoral response followed by the production of antibodies directed against the modified structures of the host (61). Some authors suggested

that long-term evolution of HCV infection might lead to an abnormal immune response (62). In addition, HCV infection is associated with a chronic inflammatory status that may contribute to this process (63).

The hypothesis of a possible molecular mimicry involved in the association between LP and HCV infection has been raised, but some authors rejected this theory (24,46). The study by Lucchese revealed an immune cross-reactivity, which could be involved in LP pathogenesis. It seems that the immunogenic peptides SSSSSS, QEQLKA, LLLLLLA, and MSLGNAG are expressed by HCV, EBV, HHV-7, HSV-1 and CMV viruses but are also found in the structure of three human proteins, pinin, desmoglein-3, and plectin, which are part of the hemidesmosome and desmosome structure (64).

The role of oxidative stress. Petti *et al* suggested that oxidative stress could underlie the relationship between OLP and HCV (27). Breaking the balance between oxidants and antioxidants can result in the alteration of immune response with consequences on defence mechanisms against HCV (27,65,66). In addition, it should be noted that there are numerous studies attesting the increased level of oxidative stress in patients with LP (67-70). Azizi and Farshchi analyzed the level of antioxidants in 48 patients with erosive OLP and revealed a significantly lower antioxidant capacity compared to healthy subjects (71). Aly and Shahin evaluated oxidative stress markers in patients with cutaneous LP, including 45 patients with LP and 45 healthy volunteers and detected an imbalance between oxidants and antioxidants. They identified increased levels of nitric oxide, malondialdehyde and superoxide dismutase; in contrast, the level of catalase was low (72).

On the other hand, studies have shown that HCV is involved in the dysregulation of the oxidant-antioxidant balance (73). HCV core protein appears to be an important regulator of mitochondrial ROS (74). The study by Khadem Ansari *et al* showed that genotypes 1a and 1b are most commonly associated with a higher level of oxidative stress, these genotypes being involved in more severe forms of disease (75).

The host immune response. Carrozzo *et al* postulated that the occurrence of OLP in HCV infected patients is related to the release of proinflammatory cytokines as a response to the presence of the virus (48). Recent research has emphasized that cytokines have an important role in the pathogenesis of OLP (10,76). In addition, polymorphism of some cytokine genes has been identified, and it has been suggested that this might underlie the genetic susceptibility of the disease (77). In line with this, Al-Mohaya *et al* reported that tumour necrosis factor (TNF)- α (-308G/A), TNF- β (+252A/G) and IL-10 (1082G/A, -819C/T and -592C/A) polymorphisms might be involved in host susceptibility to develop OLP (78).

Considering that interferon (IFN) is involved in the pathogenesis of LP, Shaker *et al* detected the presence of myxovirus resistance protein A (MxA) in tissue samples collected from patients with LP; MxA protein is a protein produced under the action of interferon. They included in the study LP patients with and without HCV infection and a control group and observed higher MxA protein levels in LP patients compared to healthy subjects and higher levels in those with infection than those without infection. The conclusion was that HCV may be involved

in the pathogenesis of LP, promoting the secretion of type 1 IFNs (79). The role of IFN in LP pathogenesis is also supported by the identification of several IFN-regulated genes in LP specimens (Mx1, IFI27, IFI30, G1P3) (80). Femiano and Scully found an increased level of TNF- α and low levels of IL1, IFN- γ and IL8 in the serum of patients with HCV infection and erosive OLP compared to those with OLP without HCV infection (32).

HCV-specific T cells capable of secreting IFN- γ were identified in oral mucosa of patients with OLP and HCV infection. In addition, CD4 and CD8 lymphocytes were more numerous in LP lesions than in peripheral blood. This demonstrates the presence of a local immune process most likely directed against epithelial cells presenting HCV antigens, a fact that might explain the role of the virus in LP pathogenesis (51). In contrast, patients with chronic hepatitis B virus (HBV) infection and OLP did not show HBV-specific T cells in oral mucosa samples (49,51).

Regulatory T cells are important players in the host immune response (81). Farid *et al* analyzed regulatory T cells in 58 patients with chronic HCV infection, 30 of them associated immune-mediated cutaneous manifestations. The most frequent skin diseases were vasculitis of small vessels and LP. They noticed that those with cutaneous manifestations had fewer regulatory T cells in the peripheral blood than those without manifestations (82).

Since HCV infection occurs in those who use injectable drugs, they are often co-infected with HIV. These patients have a low CD4 cell count, which prevents the development of an *in situ* cytotoxic response; possibly explaining the small number of cases of OLP in HIV patients (83). Campisi *et al* analyzed 104 patients with chronic hepatitis C, HIV negative and 74 HIV/HCV-co-infected patients and noted the absence of OLP in co-infected patients. However, the prevalence of OLP was also low in HCV infected patients (84).

The impact of interferon regimens. There are reported cases of worsening or *de novo* occurrence of LP lesions following therapy with interferon associated or not with ribavirin in HCV infected patients (17,85). One of the mechanisms could be the effect of IFN- α on the cascade of cytokines involved in the pathogenesis of LP (85). Nagao *et al* described a case of exacerbation of OLP in a patient with HCV infection under treatment with interferon and ribavirin. Initially, the patient received IFN- β for 2 weeks and after he continued with IFN- α -2b in association with ribavirin. After 18 weeks, the treatment was interrupted given the exacerbation of OLP lesions. The lesions improved when the therapy was discontinued (86). Grossmann *et al* reported three cases of OLP worsening after chronic hepatitis C therapy with interferon and ribavirin. They suggested that an autoimmune mechanism that was triggered by the simultaneous administration of the two drugs could be involved (87). In contrast, Doutre *et al* reported two cases of LP (one case of generalized LP and one of OLP) that improved following interferon therapy in two HCV infected patients (88).

However, the occurrence of LP after interferon therapy has also been found in patients without HCV infection. For example, Kütting *et al* described the case of a 74-year-old male treated with IFN- α for mycosis fungoides who developed oropharyngeal LP after 8 months of therapy. The lesions resolved when the therapy was discontinued (89).

Considering that IFN is involved in the occurrence of LP, IFN-free regimens are recommended for patients with LP and HCV infection (15). The effect of interferon therapy on LP lesions still remains unclear (90,91).

6. HCV infection and oral cancer

Carcinogenesis is a complex process and chronic inflammation seems to be a key factor in its development (92-96). Since OLP is a premalignant disorder, some authors paid attention to the role of HCV in its malignant transformation. According to the meta-analysis by Aghbari *et al*, 1.1% of OLP lesions progress into oral squamous cell carcinoma (OSCC) (97). It seems that HCV infection presents a 1.9-fold higher risk of oral cancer, and the association between OLP and HCV increases the risk by 3.2-fold (98). It seems that the risk of developing a squamous cell carcinoma occurs especially in HCV positive patients with long lasting OLP lesions (99). A British study that analyzed the incidence of chronic liver disease and HCV infection among patients with oral epithelial dysplasia did not reveal a positive correlation. Only two (2.6%) of the 75 patients included in the study had anti-HCV antibodies. The authors concluded that there is insufficient evidence to support the role of HCV infection in the malignant transformation of OLP lesions and the reported cases are based on a serendipitous association (100). However, some authors have detected HCV replication in samples collected from oral cancer patients (54). Furthermore, the study by Lo Muzio *et al* which included 263 patients with OLP revealed that 14 of them developed OSCC. Among the patients who developed OSCC, 3 had anti-HCV antibodies (101). In this context a multidisciplinary approach is necessary (102).

7. Conclusion

There are numerous epidemiological studies that attest to the link between LP and HCV infection, with significant geographic variations suggesting the implication of genetic and environmental factors. Regarding the mechanisms which underlie this association, several theories have been postulated, but none of them clearly explain the pathogenic pathways involved. Most studies show that the lesions are the result of the host immune response to the viral components and not the result of the direct action of the virus.

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Competing interests

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