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The Relationship between Lichen Planus and Hepatitis C in Birjand, Iran.

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Abstract:

Background: The reported prevalence of hepatitis C virus (HCV) infection in patients with lichen planus (LP) shows variations in different regions.
Objective: This study was conducted to determine the frequency of hepatitis C in Iranian patients with lichen planus at Imam reza hospital, city of Birjand, Iran.
Methods: In this case-control study, seventy three cases of lichen planus, 31 (42.5%) women and 42 (57.5%) men were diagnosed. They were recruited after obtaining a verbal consent to participate in the study and after confirmation of the diagnosis by histology. In the patients, liver function tests were performed and the patients were screened for the presence of anti-HCV antibodies. We used the prevalence of HCV antibody among 150 volunteer blood donors (age and sex matched) for comparison as the control group. An enzyme-linked immunosorbent assay (ELISA) was used to determine the presence of anti-HCV antibodies in all subjects in both groups.
Results: All patients with lichen planus had normal liver function tests. Three (4.1%) out of the 73 lichen planus group, and 1 (0.67%) out of the 150 control group were seropositive for anti-HCV Antibody. This was significantly higher than that of the control group ($p < 0.05$).
Conclusion: The results of this study suggest that a relationship exists between hepatitis C virus infection and lichen planus among Iranian patients from Birjand.

Key Words: Lichen planus, Hepatitis C, Iran.

Introduction:

Lichen planus is an inflammatory muco-cutaneous condition with characteristic violaceous polygonal flat-topped papules and plaques[1]. Pruritus is often severe. Skin, nail and hair lesions may be disfiguring, and involvement of the oral mucosa or genital mucosa in severe cases may be debilitating. LP most commonly affects middle-aged adults of both sexes, with a slight predominance in women [1, 2]. Although the aetiology of LP is unknown, immunologic and genetic factors, certain medications and some viruses have been implicated as an aetiologic agent of LP [2, 3]. An increased prevalence of chronic liver diseases has been reported in patients with LP, including primary biliary cirrhosis and chronic active hepatitis or cirrhosis of unknown origin [3-5]. Recently, a more widespread and chronic viral disease, hepatitis C (HCV), has been implicated in triggering LP. While some studies of selected populations with LP have confirmed a significant association with HCV [3, 6-9], other investigations have failed to document this finding [10-16]. This study was conducted to determine the frequency of hepatitis C in patients with LP at Imam reza hospital, city of Birjand, Iran.

Materials and Methods:

In this case-control study 73 patients with lichen planus were recruited into the study between June 2004 and March 2006. These subjects comprised of 73 patients who presented at the Dermatology Clinic of the Imam Reza Hospital in Birjand University of Medical Sciences, city of Birjand, Iran.

They were recruited after obtaining a verbal consent to participate in the study and after confirmation of the diagnosis by histology. The histological confirmation was based on the presence of degeneration of the basal layer with band like lymphocytic infiltration of the papillary dermis. Patients with suspected lichenoid drug eruptions were excluded from the study. The demographic data such as age, gender and other pieces of information including type of lesions, sites of involvement, past history of liver diseases and family history of LP were collected using a checklist. Patients were asked about risk factors for HCV, such as hemophilia, thalasemia, hemodylasis and drug-injecting addiction. None of our cases was considered positive for HCV risk factors. We used the prevalence of HCV antibody among 150 volunteer blood donors (age and sex matched) for comparison as the control group. Hepatitis C antibody titer was measured by third generation Enzyme-Linked Immunosorbent Assay (Ortho® HCV 3.0 ELISA Test System; Ortho-Clinical Diagnostics, Raritan, NJ, USA) in all subjects in both groups. Liver function tests were also performed (Pars Azmon, Iran). Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ranging between 5 to 40 IU/lit, alkaline phosphatase levels 70 to 306 IU/lit and bilirubin concentrations below 1.4 mg/dl were assumed as normal. The collected data were analyzed using SPSS (ver.12) software and chi-square test. Test of sig-

nificance were carried out at 5% level of significance.

Results:

The mean age (± SD) of the patients was 43.3± 12.8 years (patients were from ages 15–72). 42 (57.5%) patients were male and 31 (42.5%) were female. The mean age (± SD) of volunteer blood donors was 41.9± 11.5 year. 87 (58%) of volunteer blood donors were male and 63 (42%) were female. The male: female ratio in patients with lichen planus was 1.35: 1. The location of LP lesions was as follows: 45 (61.6%) were found on the trunk and extremities, 29 (39.7%) on the extremities, six (8.2%) on the face and four (5.4%) on the oral mucosa without skin involvement. There was involvement of hair in seven cases (9.6%), nails in 11 cases (13.6%) and mucosa with skin involvement in 29 cases (39.7%). The observed lesion types were as follows: generalized in 39 patients (53.4%), nonerosive mucosal in 31 patients (42.5%), actinic in 16 patients (21.9%), hypertrophic in 15 patients (20.5%), annular in 13 patients (17.8%), nail lesions in 11patients (13.6%), palmoplantar in 8 patients(10.9%), follicular in 7 patients (9.6%), atrophic in 6 patients (8.2%), pigmented in 4 patients (5.5%), erosive mucosal lesions in 2 patients (2.7%), and guttate form in 5 patients (6.8%). Eight patients (11.1%) had positive family history of LP.

Three (4.1%) out of the 73 lichen planus group, and 1 (0.67%) out of the 150 control group were seropositive for anti-HCV Antibody. This was significantly higher than that of the control group ($p < 0.05$).

Patients had no history of liver disease, with no positive findings from liver function tests. The clinical and laboratory characteristics of patients with Lp and HCV are detailed in table 1.

Table 1- Clinical and laboratory characteristics of patients with LP and HCV

Patient No	Sex/Age	LP clinical form	LFT	History of transfusion and other risk factor for HCV infection
1	M /47y	hypertrophic / non-erosive mucosal	N	No
2	F /31y	Nonerosive mucosal / Generalized	N	No
3	M /53y	Actinic	N	No

F: Female, M: Male, y: Years, N: Normal, LFT: Liver function Test.

Discussion:

Lichen planus (LP) is classified as a papulosquamous disease[15]. The etiology of LP is unknown, although many studies have investigated and supported an immunologic pathogenesis. Lymphocytes, particularly T-cells, play a major role [1, 3, 17]. Other factors include antigen-presenting cells, adhesion molecules and inflammatory cytokines. While most cases of LP are idiopathic, some are linked to medication use or hepatitis C virus (HCV) infection [2, 3, 18]. Although the manner in which HCV infection predisposes patients to the development of LP remains unclear, some speculate that long-term infection may lead to an aberrant immunologic response [3, 19]. Oral lichen planus (OLP) is an autoimmune disease produced by T lymphocyte attack on basal epithelial cells[18]. While it has been suggested that LP might be triggered by HCV, no evidence of the viral infection has been found at the site of mucocutaneous involvement [7, 8]. In recent years, both mucosal and cutaneous lichen planus have been reported to occur in the setting of chronic HCV infection [14]. However, there are wide geographical variations in the reported prevalence of HCV infection in patients with LP, varying from 0% in England 20 to 63% in Japan [21]. The available reports indicate that the prevalence of HCV antibodies in patients with mucosal and cutaneous LP is significantly higher than that of the control populations (non-LP dermatologic patients or population of blood donors) in Germany [8], Italy [22],Thailand [23], Taiwan [24], Spain [3,9], the USA [6] and Japan [21]suggesting an etiologic role for HCV in LP. However studies in Nigeria [10], France [11, 12], Mexico [16], Serbia [25], Brazil [26] and England [13, 17, 27] could not demonstrate a statistically significant association between HCV and LP.

In other hand, different studies have estimated the seroprevalence of HCV antibody among the general population (blood donors, mostly) to be about 0.16–6% world-wide[28- 29] . This figure is estimated to be less than 0.2% among Iranian blood donors, using complementary immunoblot HCV-Ab, according to the annual Iranian Blood Transfusion Organization (IBTO) internal report of 1995[29].

The pathogenic role of HCV in the development of LP is still unclear. For some authors the association of LP and positive serology for HCV, even positive RNA is not a substantive enough reason to determine the role of HCV in the pathogenesis of LP. Nevertheless, demonstration of HCV RNA in epithelial cells of oral mucosa [22, 30] and skin lesions [14] of patients with LP would lead to the theory that direct action of the virus is involved. HCV could be a potential antigen presented by Langerhans cells, followed by activation and migration of lymphocytes resulting in damage to basal cells via cytockines of cytotoxic T cells [22, 31]. The virus may alter epithelial antigenicity at sites of mucocutaneous replication leading either to direct activation of cytotoxic T cells [13, 31] or to production of antibodies against epithelial antigens [32]. Petruzzi et al [33] demonstrated differences in lymphocyte subpopulations between HCV positive oral LP patients and HCV negative patients with oral LP. They attributed this to the chronic antigenic stimulation of HCV. On the other hand, the different results in previous studies and the differ-

ences in respect to the geographic area could be in relation to the different genetic susceptibility of the hosts. Carrozzo et al [34] have suggested that genetic polymorphism of interferon-gamma and tumor necrosis factor-alpha may contribute to the development of oral and orocutaneous involvement, respectively.

Recently, lukac et al [35] determined the presence of circulating autoantibodies to desmoglein (Dsg) 1 and Dsg 3 in patients with oral lichen planus. Serum concentrations of circulating autoantibodies to Dsg 1 and Dsg 3 were determined by ELISA in 32 patients with erosive form and 25 patients with reticular form of oral lichen planus, 13 patients with acute recurrent aphthous ulcerations and 50 healthy controls. Indirect immunofluorescence analysis was also performed. Concentrations of circulating autoantibodies to both Dsg 1 and Dsg 3 detected in the sera of patients with erosive form of oral lichen planus were significantly increased in comparison with those in healthy controls, patients with recurrent aphthous ulceration, and those with reticular oral lichen planus ($P<0.001$ for both anti-Dsg autoantibodies). Indirect immunofluorescence also revealed significantly more positive findings in patients with erosive oral lichen planus (18 positive of 22 tested) than in healthy controls (1 positive of 20 tested; $P<0.001$), patients with recurrent aphthous ulceration (1 positive of 10 tested; $P<0.001$), and those with reticular oral lichen planus (3 positive of 15 tested; $P<0.001$). They have suggested that humoral autoimmunity seems to be involved in the pathogenesis of oral lichen planus. The differences in the serum concentration of desmoglein autoantibodies suggested that pathological mechanisms in erosive and reticular forms of oral lichen planus might not be the same. Oral lichen planus can undergo malignant transformation that may be linked to an increased proliferative activity and decreased apoptosis rate of the epithelial cells, phenomena that may be influenced by the inflammatory infiltrate[36].

Bascones-Ilundain et al [36] assessed the quantitative importance of apoptosis in the inflammatory infiltrate of OLP and to discuss its influence on the persistence of this infiltrate and on the malignant transformation of this disease. In [32] patients with OLP and 20 controls, apoptosis was studied by TUNEL assay and caspase-3 determination, while cell cycle arrest and senescence were studied by measurement of p21 expression. There was a low frequency of lymphocytic apoptosis according to both TUNEL (34.5% of cases negative, 65.5% with mild expression) and caspase-3 expression (42.9% of cases negative, 50% with mild expression) findings. P21 expression was also negative (9.7% of cases) or mild (80.6% of cases) in most cases. The absence or low rate of apoptosis observed in inflammatory cells in OLP appears to contribute to the persistence of the inflammatory infiltrate, potentiating the onset of molecular disorders in epithelial cells and favouring cancer development.

According to our study, a relationship exists between hepatitis C virus infection and lichen planus among Iranian patients. Our results agree with findings of other studies in different region of the world [3, 6-9, 21-24]. Contrary our results, studies in Nigeria [10], France [11, 12], Serbia

[25], Brazil [26] and England [13, 17, 27] could not demonstrate a statistically significant association between HCV and LP. Rahnama et al [15] found that HCV antibody prevalence in their patients with LP (1.5%) in Kerman, Iran was lower than that of the control group (3.7%) and the difference was not statistically significant. Erkek et al [14] found that HCV antibody prevalence in Turkish patients with LP (12.9%) was higher than that of the control group (3.7%) but the difference was not statistically significant, whereas Kirtek et al [7] found statistically significant difference in Gaziantep region of Turkey. These contradictory results may be attributed to the high prevalence of HCV in some countries, such as Japan and southern Europe. Another possible cause is unknown epidemiological and immunological factors, such as HLA, which increase the prevalence of the association of LP with HCV in some parts of the world, such as Italy[37, 38]. In our study, patients had no history of liver disease, with no positive findings from liver function tests. These results agree with other studies [15, 25]. In a review study, Chainani etal [39] reviewed and summarized the published literature on the association between Oral LP and HCV. A search of the computerized database MEDLINE (1966-June 2003) was conducted. They found that studies on the association of OLP and HCV provide enough information to raise a number of interesting questions about this association. Important biases-including selection bias; investigator bias due to lack of blinding and the possible resultant nondifferential misclassification of disease; and possible confounding by age in the studies published-make it difficult to draw firm conclusions. However, the need for future studies that take into consideration all these factors in the study methodology is highlighted by this review. Lodi et al [40] investigated the relationship between LP and HCV seropositivity. In a cross-sectional study they tested the sera of 303 consecutive newly diagnosed patients with histologically proven LP referred to three Italian centers for the presence of anti-HCV Ab. Next, in a systematic review, studies were identified by searching different databases in April 2004. They found anti-HCV circulating antibodies are more common in patients with LP than in controls, although such an association may not be significant in some geographical areas. Recently, Podanyi et al [41] supposed that the lichen planus is one of the extrahepatic manifestations of HCV infection and there is a real correlation between the two diseases in two cases but in a review study of correlation between Hepatitis C virus and lichen planus, Lodi [42] conclude no firm conclusions can be drawn from this review.

The results of our study suggest that a relationship exists between hepatitis C virus infection and lichen planus among Iranian patients from Birjand. Considering the current evidence, it seems appropriate to screen all patients with lichen planus for HCV infection. Why studies with Iranian patients from Birjand and Kerman have contradicted each other remains a matter to be explained. More studies are necessary for a better understanding of the relationship of lichen planus and HCV infection.

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