

# Lichen planus and hepatitis C virus infection

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## ABSTRACT

**Background** The association of lichen planus (LP) with liver diseases is well established. The reported prevalence rates of hepatitis C virus (HCV) antibodies in patients with LP tend to appear quite variable.

**Objective** The aim of this study was to assess the prevalence of HCV antibodies in a group of patients with LP and evaluate the clinical characteristics of the subgroup with LP associated with HCV.

**Methods** We studied 101 patients, 57 (56.4%) women and 44 (43.5%) men with a mean age of 48 years, consecutively diagnosed with cutaneous and/or mucosal LP between January 1992 and December 2000. We used 99 age- and sex-matched controls.

**Results** Anti-HCV antibodies were detected in nine cases (8.9%) of the LP group but only two (2.02%) of the controls. The odds ratio between the subjects with HCV positivity and those with negative HCV virus was 4.74, with a confidence interval at 95%, between 0.999 and 22.545. A statistically significant association was only demonstrated between erosive LP and infection by HCV.

**Conclusions** The possibility of liver disease caused by HCV should be ruled out in patients with LP, especially in the erosive form.

**Key words:** epidemiology, hepatitis C virus, lichen planus

Received: 7 March 2002, accepted 22 May 2002

## Introduction

Lichen planus (LP) is a generally self-limiting disorder that usually appears in middle-aged adults and can affect the skin, mucosa, hair and nails. Various clinical forms, lichenoid eruptions (which are similar to LP and are normally drug induced) and association with other diseases have been described,<sup>1,2</sup> although in some cases it is not known if the association is simply due to chance. It has been maintained since the 1980s that patients with LP have a greater proportion of hepatopathies than the general population.<sup>3</sup> Depending on the various studies, the prevalence of chronic hepatic disease in LP patients oscillates between 0.1 and 35%, the majority of which are based on the determination of aminotransaminases.<sup>4</sup> In Spain hepatitis C antibody prevalence is surprisingly one of the highest in the world.

We describe a case–control study: (i) to determine the prevalence of hepatitis C virus (HCV) infection in those patients diagnosed with LP in our studied population; (ii) to study the clinical characteristics of the subgroup with LP associated with hepatitis C; and (iii) to check for a possible relation between

some of the lesion localizations or some clinical form of LP and this viral infection.

## Materials and methods

### Patients

We studied 101 patients, 57 (56.43%) women and 44 (43.56%) men, consecutively diagnosed with cutaneous and/or mucosal LP between January 1992 and December 2000. The age range of the affected patients was 4–78 years with a mean age of 48 years.

### Case definition

The diagnosis was based on the existence of typical clinical and histopathological findings of LP. Cases in which lichenoid reactions due to drugs were suspected were excluded.

The clinical diagnosis was established based on the presence of typical LP lesions, such as: (i) polygonal papulose lesions or erythematous–violaceous plaques with the

characteristic Wickham's striae; (ii) appearance of the Koebner phenomenon; (iii) localization on the wrists, ankles, lumbar region and/or lesions of an annular morphology on the penis and/or hyperkeratotic lesions in the area of the palms and soles; (iv) evolution toward a long-lasting residual pigmentation; (v) off-white hyperkeratotic lesions of a reticular morphology in the buccal mucosa; and (vi) nail lesions as longitudinal striations, onychoschizia, onychomadesis or the characteristic formation of pterygium.

The histopathological diagnosis was based on the following findings: (i) orthohyperkeratosis, acanthosis and hypergranulosis (as changes in the epidermis); (ii) band-like lymphohistiocytic infiltrate in the dermoepidermal limit; (iii) the presence of hyaline or colloid bodies corresponding to degenerated epidermal basal cells in the lower epidermis layers; and (iv) melanin pigment incontinence.

## Controls

We used a control group consisting of 99 patients treated in the same office who were matched by age and sex. Sixty-one were women (19–79 years old) consecutively diagnosed with chronic urticaria and 38 were men (13–77 years old) diagnosed with urticaria, warts, keratosis, eczema or psoriasis. The average age was 46.6.

## Methods

A protocolized clinical history was prepared in which data corresponding to the following variables were collected: (i) sex and age; (ii) localization of LP lesions in the oral cavity, wrists, feet and ankles, back, upper extremities, genitalia, axillae, abdomen, nails, scalp, facial area and other localizations; (iii) determination of the clinical form of LP, such as lichen ruber planus, oral LP, lineal LP, erosive LP, lichen planopilaris, frontal fibrosing alopecia, annular LP, hypertrophic LP, bullous LP, follicular LP tumidus retroauricular, palmoplantar LP, actinic LP and follicular LP; and (iv) hepatic diseases previously diagnosed by other physicians.

The following laboratory tests were performed: (i) the patients' serum was analysed to determine the analytic parameters of alanine aminotransferase (GPT), aspartate aminotransferase (GOT), bilirubin, alkaline phosphatase,  $\gamma$ -glutamyl transpeptidase by automated methods in a BW/Hitachi 917 Roche Diagnostic Autoanalyser; (ii) antimitochondrial antibodies were determined by immunofluorescence with triple tissue portals; (iii) determination of anti-HCV antibodies was carried out using the second generation enzyme-linked immunosorbent assay immunoenzymatic method (Ortho Diagnostic Systems); and (iv) confirmation of enzyme-linked immunosorbent assay results was performed using second-generation four-antigen recombinant immunoblot assay (Ortho Diagnostic Systems).

## Statistical analysis

The statistical analysis was applied as follows. In order to determine the possible associations among the variables of interest, the Chi-square test was used. The Fisher test was used in the study of dichotomic variables to detect possible associations. A bilateral significance level was set at  $\alpha = 0.05$ . The data collection log was implemented in Microsoft Access 97. The software used in the statistical analysis was SPSS version 9.0 and Microsoft Excel 97. All these tools were used in a Pentium 133 MHz with 32 Mb of RAM.

## Results

### Prevalence of anti-hepatitis C virus antibodies

Anti-HCV antibodies were detected in nine cases (8.9%). In the control group we detected only two positive cases (both with chronic urticaria) for anti-HCV antibodies (2.02%) of the 99 studied.

From a statistical viewpoint, the association between cases/controls and the hepatitis C is statistically significant ( $P = 0.05$ ). The odds ratio between the subjects with C virus positivity and those with negative C virus was 4.74, with a confidence interval at 95%, between 0.999 and 22.545.

### Patients with lichen planus and hepatitis C

#### Age and localization

The characteristics of the nine-patient group with hepatitis C (six males and three females) from 19 to 78 years old (average age 55.5 years) were analysed. In this subgroup of patients with LP and hepatitis C, lesions localized in the buccal region, seven cases (77%), the back, three (33%), wrists, three (33%), feet and ankles, two (22%), palmoplantar, two (22%), arms, one (11%) and other areas, two (22%), predominated.

In the group with HCV and LP, oral localization and on the wrists, back, feet and ankles and palmoplantar was frequently observed; nevertheless, when the Fisher test was applied no statistically significant differences were found between the lesion localization in the patients with LP and positive C virus and those that had LP and negative C virus (Table 1).

### Clinical forms of lichen planus

In the group with anti-HCV antibodies, the diagnosed clinical forms of LP corresponded to lichen ruber planus in four cases (44.4%), to erosive LP in four (44.4%) and to hypertrophic LP in one case (11.1%). The clinical data of these nine patients is detailed in Table 2.

A statistically significant association was only demonstrated between erosive LP and infection by HCV (Table 3).

## Discussion

In recent years the association of hepatic diseases and especially hepatotropic virus with LP has been described. The first case of 0 in which a patient presented LP with hepatitis C following 10 months of treatment with interferon- $\alpha$  was later reported,<sup>6</sup> along with other isolated cases of this association.<sup>7–12</sup>

Jubert *et al.*<sup>8</sup> described six patients with LP (four had erosive mucosal erosions) and a liver disease caused by HCV, demonstrated by the presence of viral RNA in serum. A 5% prevalence of LP in a series of 61 patients with active chronic hepatitis activated by HCV was detected. These data were confirmed in more in-depth studies. In Spain, numerous series with a variable prevalence of antibodies for C virus that oscillated between 10.5

and 47% as opposed to 2–5% for the control group<sup>13–18</sup> have been published. In other countries, in the Mediterranean area<sup>19,20</sup> as well as in other regions,<sup>21,22</sup> similar data have been found.

However, other epidemiological studies undertaken in France, Turkey and in Great Britain have not demonstrated a significant difference between the prevalence of anti-HCV antibodies in LP patients and control groups.<sup>23–26</sup> A British study of 180 cases of oral LP did not show an association with hepatic disease.<sup>27</sup>

We have detected in our revision that 8.9% of the LP cases have anti-HCV antibodies, which signifies the lowest prevalence found in the Spanish studies, where it oscillates between 10.5% and 47%.<sup>13–18</sup> One outstanding note is that in three of them the diagnosis of hepatitis C was established based on the dermatological symptoms. These differences may be due to the fact that in some of them retrospective studies have been made, or that the diagnosed subjects were included after revising the histological diagnosis for hepatitis C, or that the sample was small. Another possible explanation is the different hepatitis C infection prevalence rate in our area compared with other areas where it is higher.<sup>13,15,22,28,29</sup>

LP normally appears in persons between 50 and 70 years old. In our study the average global age was 55 for the group with hepatitis C, and males were more affected (six cases cf. three in females). In the revision of Sánchez-Pérez *et al.*<sup>15</sup> LP associated with hepatitis C occurred more frequently in those subjects who were 70–90 years old; however, they demonstrated that females were doubly affected in comparison with males.

It is described that between 30 and 70% of patients with classic LP have mucosal involvement.<sup>2</sup> We found an oral

**Table 1** Lichen planus lesion localization

Localization	Hepatitis C virus		P value ( $\alpha = 0.05$ )
	(+) n (%)	(-) n (%)	
Oral lichen planus	7 (77%)	46 (50%)	0.165
Localization wrists	3 (33%)	38 (41%)	0.735
Arms	1 (11%)	17 (18%)	1.000
Inferiors	1 (11%)	17 (18%)	1.000
Axillae	0	9 (9%)	1.000
Back	3 (33%)	22 (23%)	0.686
Genitalia	0	12 (13%)	0.594
Feet–ankles	2 (22%)	26 (28%)	1.000
Palmoplantar	2 (22%)	26 (28%)	0.608
Scalp	0	6 (6%)	1.000
Facial area	0	4 (4%)	1.000
Abdomen	0	9 (9%)	1.000

**Table 2** Patients with lichen planus (LP) and hepatitis C (HCV)

Patient no.	Age	Sex	LP clinical form	Diagnosed previously HCV	Induced or aggravated by interferon
1	55	Female	Hypertrophic	No	
2	78	Male	Lichen ruber planus	Yes	
3	54	Male	Erosive	No	Yes
4	78	Male	Lichen ruber planus	Yes	
5	62	Female	Lichen ruber planus	Yes	
6	62	Male	Erosive	Yes	
7	37	Male	Erosive	Yes	Yes
8	19	Male	Lichen ruber planus	No	
9	54	Female	Erosive	Yes	Yes

**Table 3** Relation of clinical form of lichen planus (LP) and infection by hepatitis C virus (HCV)

Clinical form	HCV+ n (%)	HCV- n (%)	Statistics Fisher P value ( $\alpha = 0.05$ )	Odds ratio (Confidence interval 95%)
Erosive LP	4 (44.44%)	2 (2.2%)	0.001	36 (5.27, 245.91)
Lichen ruber planus	4 (44.44%)	52 (56.5%)	0.507	0.61 (0.15, 2.44)
Hypertrophic LP	1 (1.1%)	1 (11.1%)	0.171	11.37 (0.64, 199.51)

involvement in 52% of the patients with cutaneous LP that rose to 77% in the group with LP associated with HCV infection.

The clinical forms of presentation in the group of nine patients with positive HCV as opposed to those with negative C virus were four cases of lichen ruber planus (44.4% against 55.4%), four of erosive LP [44.4% against two (2.1%)] and one case (11.1%) of hypertrophic LP in contrast to 1% in the group of 92 patients with negative HCV. A statistically significant association between the erosive form of LP and HCV infection was demonstrated.

These results appear to confirm those suggested by other studies, which demonstrate that erosive LP is more frequent in patients with LP associated with hepatic disease or other diseases;<sup>30–33</sup> a statistically significant association exists between erosive LP and HCV infection.<sup>15,16</sup> Miralles *et al.*<sup>13</sup> found that of 13 patients with LP and positive HCV, eight had oral mucosal involvement, five of which had an erosive form. Mignogna *et al.*,<sup>34</sup> on the other hand, found that among 263 patients with oral LP the reticular form was more frequent in the carriers of HCV than in those who tested negative, while the plaque form was more prevalent in the latter. There were no significant differences in the erosive or atrophic forms. The asymmetrical localization in buccal mucosa and the localizations on the tongue, labial and gingival mucosa were more common in the cases with HCV, in which, furthermore, cutaneous involvement is less prevalent.

For some authors the association of LP and positive serology for HCV as well as for positive RNA is not a substantive enough reason to determine the role of HCV in the pathogenesis of LP. Nevertheless, the recent demonstration of RNA of HCV in epithelial cells of the oral mucosa of patients with LP would lead to the theory that direct action of the virus is involved.<sup>35</sup> HCV could be involved, among other factors, in the pathogenesis of LP (acting as an exogenous antigen or due to the presence in the keratinocytes of common epitopes similar to that of the hepatocytes damaged by this hepatotropic virus). No relation between the different genotypes of HCV and the presence or absence of LP lesions has been demonstrated.<sup>36,37</sup> The differences with respect to the results could be in relation to the different epidemiological methods and, perhaps, in aspects of a genetic type relative to the host, as has been recently demonstrated.<sup>38</sup>

In conclusion, the possibility of liver disease caused by HCV should be ruled out in patients with LP (especially in the erosive form) if there is an alteration of the hepatic function tests or if there is no other apparent cause.

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