

# Association between lichen planus and hepatitis C virus infection: a prospective study with 66 patients of the dermatology department of the hospital Santa Casa de Misericórdia de São Paulo\*

## *Associação entre líquen plano e infecção pelo vírus da hepatite C: um estudo prospectivo envolvendo 66 pacientes da clínica de dermatologia da Santa Casa de Misericórdia de São Paulo\**

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**Abstract:** BACKGROUND - Lichen planus is a chronic inflammatory dermatosis of unknown etiology. Its association with liver diseases, particularly hepatitis C, has been widely approached since 1990, when serology for the detection of hepatitis C virus became available.

OBJECTIVES - The objective of this study was to evaluate a possible causal relation between virus C infection and lichen planus.

METHODS - Sixty-six patients with lichen planus seen at the Dermatology Department of Santa Casa de Misericórdia de São Paulo from 2000 to 2003 were included in the study group. The control group comprised volunteer blood donors of the Blood Bank of Santa Casa de Misericórdia de São Paulo, from October 2001 to October 2002.

RESULTS - Five out of the 66 patients with lichen planus had a positive serology for HCV, representing 7.5% in comparison with 0.69% of the blood donors.

CONCLUSION - Our findings are consistent with those reported in the medical literature. However, further studies are necessary to improve our knowledge on such a controversial relation.

Keywords: Hepatitis C; Lichen planus; Hepacivirus

**Resumo:** FUNDAMENTOS - O líquen plano é dermatose inflamatória crônica de etiologia desconhecida. Sua associação com doença hepática, particularmente a hepatite C, é tema de diversos trabalhos em todo o mundo, desde 1990, quando a sorologia para detecção do vírus da hepatite C (VHC) se tornou disponível.

OBJETIVOS - Este estudo visa avaliar uma possível relação causal entre a infecção pelo vírus C e o líquen plano.

MÉTODOS - Tomaram-se por grupo de estudo 66 pacientes com líquen plano matriculados na Clínica de Dermatologia da Santa Casa de Misericórdia de São Paulo, no período de 2000 a 2003. O grupo comparativo foi constituído pelos doadores de sangue voluntários do Banco de Sangue da Santa Casa de Misericórdia de São Paulo, durante o período de outubro de 2001 a outubro de 2002.

RESULTADOS - Dos 66 pacientes com líquen plano, cinco apresentaram sorologia positiva para VHC, representando 7,5% em comparação com 0,69% dos doadores de sangue.

CONCLUSÕES - Esse resultado é compatível com muitos dados contidos na literatura médica mundial. Entretanto, são necessários novos estudos para o melhor conhecimento dessa controversa relação.

Palavras-chave: Hepatite C; Líquen plano; Hepacivirus

## INTRODUCTION

Lichen planus is a chronic inflammatory dermatosis with characteristic clinical and histopathological features. However, its etiology and pathogenesis remain obscure. Some hypotheses have been suggested. A viral origin is considered because inclusion bodies are found at electron microscopy. Other causes suggested are genetic predisposition (familial occurrence), and psychogenic, immunological and neurological disorders.<sup>1</sup> Recently, chronic liver diseases of varying causes have been studied as possible etiologic factors of lichen planus.

The prevalence of chronic liver disease in lichen planus varies considerably in the medical literature.<sup>2-4</sup> A multicenter study including 577 Italian patients with lichen planus showed that they had two-fold higher risk of presenting liver alterations when compared to the general population. These alterations range from a simple increase in transaminase levels to liver cirrhosis. The risk of these patients presenting chronic liver disease was not influenced by variables such as age, gender, alcohol consumption or hepatitis B virus infection.<sup>5</sup> This fact suggests that the

Received on March 07, 2005.

Approved by the Consultative Council and accepted for publication on August 05, 2005.

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relation between lichen planus and the causes of chronic liver disease should be investigated. In the past decade a possible etiologic role has been attributed to hepatotropic viruses, especially C virus.<sup>4</sup>

Hepatitis C virus (HCV) is a RNA virus identified by Choo et al., in 1989. One hundred and seventy million individuals are estimated to be infected with HCV worldwide,<sup>6,7</sup> and 3.2 million of them are in Brazil.<sup>8,9</sup> It is, therefore, one of the major public health problems faced all over the world.

After exposure to the virus, infected individuals go through an incubation period that could range from one to five months. Thirty to 40% of adults with acute HCV infection have mild symptoms, predominantly fever, malaise, fatigue, nausea, vomiting, and slight abdominal pain.<sup>8,9</sup> Thus, the transition from the acute to the chronic phase may go unnoticed. Chronic HCV hepatitis is asymptomatic or oligosymptomatic in most cases. Generally, clinical manifestations occur in later phases of the disease. Hence, diagnosis is often made by chance when blood tests are requested for other purposes. HCV is the major etiologic agent of non-A non-B chronic hepatitis and it is mainly parenterally transmitted. The following groups are considered at a higher risk for HCV infection: individuals who received blood transfusion or blood products before 1993, intravenous drug users, hemophiliacs, individuals with piercings or tattoos, and individuals with other forms of percutaneous exposure. Sexual transmission is less frequent and occurs in individuals with multiple partners. Vertical transmission is rare when compared to that of hepatitis B.<sup>10</sup> Laboratory diagnosis of hepatitis C, as well as of the resulting liver disease, is made in stages. The investigation starts with the performance of HCV serology. AntiHCV-positive patients are tested for qualitative PCR (polymerase chain reaction): 25% of them are negative and are considered cured. The 75% positive cases are tested for liver diseases by means of transaminase levels. If transaminases are elevated, a liver biopsy should be indicated. Individuals with moderate or severe liver disease should be tested for virus C genotype to define prognosis and treatment. The treatment of hepatitis C is difficult and expensive. The main drugs used are interferon and ribavirin.<sup>11</sup>

HCV infection only started to be considered a possible etiologic agent of lichen planus when HCV serology became available, in 1990. The first case of a patient with lichen planus confirmed by biopsy and active HCV hepatitis was described in France, in 1991. Studies suggest that skin and mucosal lesions may be caused by direct action of the virus or by an induced immunological response, especially when erosive oral lesions are present.<sup>2</sup> However, the medical literature data vary much as regards the preva-

lence of hepatitis C in patients with lichen planus. The figures obtained range from 4%, in France, to 65%, in Japan.<sup>2</sup> Recent controlled studies conducted in the United States, Italy, Japan and Germany<sup>5,12,13</sup> demonstrated the relation between virus C infection and lichen planus, suggesting that HCV may be involved in the development of this skin condition, mainly of the oral subtype. Concurrently, a low prevalence in HCV infection in patients with lichen planus was found in studies conducted in England and France.<sup>12,14,15</sup> This discrepancy may be justified by variability in prevalence of hepatitis C in the world population, which, in the literature, ranges from 0.3% to 1.5%, depending on the country.<sup>16</sup> Wide variations occur even within the same country, according to the region. In Brazil, prevalence data of C virus infection show that the distribution ranges from 0.65%, in the Southern Region, to 2.12%, in the Northern Region. In the Southeastern Region the mean prevalence is 1.43%.<sup>10</sup> Some authors suggest that the higher prevalence of C virus in some regions may interfere in the results of the studies, that is, studies carried out in countries with a higher prevalence of HCV will have a significant association between lichen planus and hepatitis C.

A study conducted in Japan<sup>17</sup> investigated the occurrence of oral lichen planus in patients with chronic hepatitis C treated with interferon; six (2.2%) out of 275 developed oral lichen planus during the treatment. In contrast, the development of oral lichen planus was not observed in any of the 230 patients with chronic hepatitis C who were not treated with interferon, which resulted in a significant difference between the two groups ( $p < 0.05$ ). Moreover, four out of the six patients who developed oral lichen planus showed a complete response to treatment with interferon, with normalization of transaminase levels and reduction of viral RNA to undetectable levels. In addition, three out of these six patients developed oral lichen planus when the HCV RNA was already at undetectable levels. These results suggest that maybe the direct action of the virus is not important in the pathogenesis of oral lichen planus (OLP) in patients with hepatitis C. On the other hand, immunological alterations determined by interferon could be relevant for the development of OLP in patients with HCV infection.

As already mentioned, some studies demonstrated a significant causal relation between HCV and lichen planus, and some reported the opposite. Several authors have developed epidemiological studies with different population groups to clarify the existence of such relationship. In the Brazilian literature only three studies on this subject are found, two of which conducted in Rio de Janeiro,<sup>4,18</sup> and one in

Sao Paulo.<sup>19</sup> The latter showed a significant association of oral lichen planus and HCV infection. Given the small number of local studies, we proposed the analysis of the prevalence of hepatitis C virus infection in patients with lichen planus seen at the Dermatology Department of *Santa Casa de São Paulo*, comparing it to the prevalence of hepatitis C virus infection in blood donors of the Blood Bank of *Santa Casa de São Paulo*.

## MATERIAL AND METHODS

The present study was conducted at the Dermatology Department of Santa Casa de Sao Paulo. All patients diagnosed with lichen planus confirmed by histopathological examination, seen at this service from 2000 to 2003, were included in the study. Sixty-six adult patients were enrolled. Serology for hepatitis C virus with ELISA was requested for all patients. HCV positive cases were confirmed by repetition of the test (Group 1).

The control group was composed of volunteer blood donors of the Blood Bank of *Santa Casa de Misericórdia de São Paulo* (44947 patients) of both sexes, age range 18-65 years, from October 2001 to October 2002. These patients were tested for the Blood Bank routine tests, including serology for hepatitis C using ELISA (Group 2).

The Student's *t* test for proportions, controlled by the Levene's test for equality of variances, was used for the statistical analysis to compare simple arithmetic means of proportions of both groups considered. A 95%-confidence interval was attributed to each prevalence. The parameter  $p < 5\%$  (0.050) was used to determine a statistically significant difference. The SPSS - V. 10.0 software was used for calculations and analysis of results.

## RESULTS

Group 1 (patients with lichen planus) - Of the 66 participants in this group, 34 (51.5%) were females and 32 (48.5%) were males. The predominant age range for both sexes was 31-40 years (Table 1).

The clinical presentation of lichen planus varied with predominance of exclusively skin lesions in 54 patients (81.8%). Of the total number of patients, nine (13.6%) had skin and mucosal lesions, five of which had oral lesions and four had genital lesions. None of these patients had both forms concomitantly. Three patients (4.5%) had exclusively mucosal lesions, two of them had genital lesions and one had both genital and oral lesions concomitantly (Table 2).

Five patients had positive serology for HCV ( $7.5\% \pm 0.27$ ). Two of them (40%) were females and three (60%) were males. Regarding age range distribution, one patient (20%) was in the range 30-39 years, two (40%) were 40-49 years, and two (40%) were 50-59 years (Table 2). The predominant clinical presentation in these patients was the exclusively cutaneous form: the five patients (100%) had this type of lesion (Table 3).

The time elapsed from the onset of the first lichen planus lesion to the first visit to the Dermatology Department of *Santa Casa de São Paulo* ranged from one week to 13 years, with an 11.8-month mean interval. Considering only the five patients with lichen planus and positive serology for HCV, the shortest interval reported was four months, and the longest, 13 years, with a mean of 3.6 years.

Group 2 (blood donors) - From October 2001 to October 2002, 44947 blood collections were performed, of which 310 ( $0.69\% \pm 0.08$ ) were positive for HCV.

Comparing the percentage of patients with a positive serology for HCV in Group 1 ( $7.58\% \pm 0.27$ ) and in Group 2 ( $0.69\% \pm 0.08$ ), a significant difference is observed, with  $p = 0.040$ .

## DISCUSSION

Although lichen planus was described more than a century ago, its etiology remains little known.<sup>4</sup> Many factors have been suggested for the pathogenesis, such as immunological mechanisms, genetic characteristics, drug use, and infections, particularly viral infections. The association between lichen planus

**TABLE 1:** Sex and age range distribution of 66 patients with lichen planus seen at the Dermatology Department of Santa Casa de Misericórdia de São Paulo - 2000 to 2003

Age range	Females		Males		Total	%
	N	%	N	%		
0 - 9	-	-	-	-	-	-
10 - 19	-	-	3	4.5	3	4.5
20 - 29	5	7.6	6	9.2	11	16.8
30 - 39	11	16.7	12	18.2	23	34.9
40 - 49	4	6.1	7	10.6	11	16.7
50 - 59	9	13.6	3	4.5	12	18.1
60 - 69	5	7.5	1	1.5	6	9
Total	34	51.5	32	48.5	66	100

**TABLE 2:** Age range and sex distribution of five patients with lichen planus and positive serology for HCV seen at the Dermatology Department of Santa Casa de Misericórdia de São Paulo - 2001 to 2003

Age range	Female		Male		Total	%
	N	%	N	%		
0 - 9	-	-	-	-	-	-
10 - 19	-	-	-	-	-	-
20 - 29	-	-	-	-	-	-
30 - 39	-	-	1	20	1	20
40 - 49	1	20	1	20	2	40
50 - 59	1	20	1	20	2	40
60 - 69	-	-	-	-	-	-
Total	2	40	3	60	5	100

**TABLE 3:** Lesion distribution in 66 patients with lichen planus seen at the Dermatology Department of Santa Casa de Misericórdia de São Paulo and correlation with positive serology for HCV - 2000 to 2003

Type of lesion	Number	%	Number of positive serologies for HCV	% of total positive serologies for HCV
Exclusively cutaneous	54	81.8	5	100
Cutaneous and mucosal	9	13.6	-	-
Genital	4	-	-	-
Oral	5	-	-	-
Both	-	-	-	-
Exclusively mucosal	3	4.6	-	-
Genital	2	-	-	-
Oral	-	-	-	-
Both	1	-	-	-

and hepatitis C virus has been frequently reported; however, the causal relation between these two conditions has not yet been clearly established. Some authors suggested that lichen planus lesions may be caused by viral replication in the skin and mucosa or a result of an immune reaction mediated by HCV.<sup>4,20</sup>

The statistically significant difference (p=0.040) between the prevalence of HCV infection among patients with lichen planus (7.5% ± 0.27) and among the control group (0.69% ± 0.08) found in the present study is consistent with the results found in many studies in the medical literature.<sup>4,12,15,20,21</sup> Nonetheless, a wide variation in data obtained in different countries was observed.

The influence of geographic origin of the patients on the study results is suggested.<sup>2,22</sup> For instance, in Italy, the prevalence of HCV infection reaches high levels when compared to those of the rest of the world population, ranging from 0.7 to 1.3%.<sup>3</sup> Studies conducted in that country showed a significant association between lichen planus and a positive serology for hepatitis C virus.<sup>12,15</sup> The same was observed in a case control study conducted in Iran, in which patients with lichen planus were compared to blood bank donors.<sup>22</sup> On the other hand, studies conducted in Great Britain and in the Netherlands, where the prevalence of HCV infection is lower (0.088-0.55% and 0.7%, respectively), did not show a significant association.<sup>3,12,15</sup> The wide variability

in the prevalence of HCV infection in the world population may explain such contradictory results.

It should also be mentioned that in the regions with a higher prevalence, HCV infection is more frequent in individuals older than 40 years and uncommon in those aged under 20 years.<sup>5</sup> This fact suggests that the prevalence of HCV infection may be related to the time of exposure of the individual to procedures or activities with risk of virus contamination. In the present study, four out of the five patients with lichen planus and positive serology for HCV were aged over 40 years. This makes us question a causal relation between HCV and lichen planus because patients with lichen planus who are over 40 years had higher chances of exposure to HCV and therefore a higher possibility of contamination, so that the association is pure coincidence.

In Brazil, the Ministry of Health estimates that chronic cases of hepatitis C may correspond to 1.5% of population.<sup>10</sup> However, hepatitis C was only definitely classified as a compulsorily notifiable disease in 1999, and basic training in epidemiological surveillance only started in 2002.<sup>10</sup> Thus, more reliable data on this subject have become available only recently. A study performed in São Paulo<sup>19</sup> analyzed the prevalence of HCV infection among patients with oral lichen planus at *Faculdade de Odontologia da Universidade de São Paulo* [Dentistry School of Universidade de São Paulo] (8.8%) and compared it

**TABLE 4:** Patient distribution in groups 1 and 2 by hepatitis C virus serology result

	<b>Group 1</b>		<b>Group 2</b>	
	Patients with Lichen Planus		Blood Bank Donors	
Positive serology for HCV	05	7.58%	310	0.69%
Negative serology for HCV	61	92.42%	44,637	99.04%

Positive serology for HCV for patients with lichen planus was significantly higher than for Blood Bank donors ( $p < 0.05$ )

to the prevalence in the general population of the City of Sao Paulo, currently estimated at 1.43%,<sup>19,23</sup> this rate may be considered high if data from the international literature are taken as a reference.

Some authors suggest that the association between lichen planus and hepatitis C may result from infection with a particular form of HCV, a genotype found only in certain geographic areas. Since HCV was identified, six different types and some subtypes of genotypes have been described (1a, 1b, 2a, 2b, 3, 4, 5a, 6a). Genotype 1 is more frequent than non-1 genotypes (60% versus 40%). For this reason, many authors have unsuccessfully attempted to identify a specific HCV genotype that could be responsible for the development of lichen planus.<sup>14,18</sup> A study conducted in Denmark<sup>9</sup> determined the genotypes of 39 patients with lichen planus infected with HCV. Of the 33 patients with detectable viremia, 17 (51%) had infection with subtype 1b, nine (27%) with subtype 2a, two (6%) with subtype 1a, and one (3%) with subtype 2b. The genotype could not be determined in four patients. However, this frequency distribution of HCV genotypes was similar to that described in an Italian study with HCV positive patients in whom the presence or absence of lichen planus was disregarded. Thus, the authors concluded that the association between lichen planus and HCV infection was not due to a particular virus genotype.<sup>6</sup>

At this point, it is worth discussing the identification method of HCV infection. The present study, like most other studies available in the literature, was based exclusively in serologic evidence of hepatitis C virus infection. However, this method is known to be subject to errors, and false-positive and false-negative results may occur. Currently, the confirmation of positive serology for HCV has become possible with the detection of viral RNA. More recent studies have used this technique to confirm HCV infection in the patients studied, and even as an attempt to detect virus C RNA in biopsies of lichen planus lesions.<sup>24</sup>

Another important consideration that should be made concerns the clinical presentation of lichen planus that is the most frequently associated with HCV infection. In a literature review we can observe that the clinical presentation of lichen planus most frequently associated with HCV infection is the ero-

sive type in oral mucosa. Some studies showed that HCV may be identified in oral mucosa epithelium cells and in oral lichen planus lesions of patients with positive serologies.<sup>21</sup> A study with Italian patients found a significant association between HCV and exclusively oral lichen planus and HLA-DR6 allele, suggesting that, more than the virus itself, the host could influence in progression of the disease.<sup>14</sup> None of the patients analyzed in the present study had this clinical presentation of the disease.

Another interesting and controversial point is the influence of the treatment of hepatitis C with alpha interferon in the development of lichen planus. This drug has an antiviral and immunomodulating activity. In some patients, it may exacerbate inflammatory skin conditions that were at a low activity level prior to initiation of treatment. This reaction would be triggered by the production of lymphokines and by the expression of adhesion molecules in the skin, induced by the drug.<sup>15,16,20,26,27</sup> In other patients, however, lichen planus may improve or even resolve after alpha interferon therapy.<sup>15,16,28</sup>

## CONCLUSIONS

In conclusion, a statistically higher prevalence of HCV infection was found among patients with lichen planus, seen at the Dermatology Department of Santa Casa de Sao Paulo, when compared to blood donors of the same hospital. Further studies are necessary to elucidate such a controversial relation. There may be some suggestions, such as to stratify age range in the control group, to conduct case control studies, to verify the origin of the patients studied, to use PCR techniques to confirm the diagnosis of HCV infection, to investigate the relation between treatment of hepatitis C and the progression of lichen planus lesions, and to study the relation between different genotypes of HCV and lichen planus in different countries. The need for further studies is justified by the fact that this skin condition may be the first manifestation of a systemic disease with a significant morbidity and mortality.

Thus, a careful history taking is encouraged, with emphasis in risk factors for chronic liver diseases in patients with lichen planus. □

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