Research Article

Analysis of association between lichen planus with hepatitis B and hepatitis C virus infection in patients attending outpatient department of dermatology at tertiary care hospital in Central Rajasthan

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ABSTRACT

Background: Lichen planus (LP) is a non-infectious cutaneous disease, characterized by the presence of itchy, flat from top, polygonal, and papular lesions having a strikingly violaceous color. **Objectives:** The objectives are as follows: (1) To establish the association of hepatitis B and hepatitis C with LP in urban areas of Ajmer and (2) to analyze the derangements in liver function tests of LP patients who attended the outpatient Department of Dermatology in JLN Hospital Ajmer. **Materials and Methods:** To conduct the study, 102 patients of LP and 100 control subjects were selected between age groups of 18 and 60 years. A detailed history including age, sex, race, residence, clinical symptoms, and their duration was recorded. Control group was selected from blood donors at blood bank of Jawaharlal Nehru Medical College, Ajmer, and was corresponding in age and sex to those of study group. A thorough clinical examination, systemic and cutaneous examination was performed. Clinical findings classical of LP and lesions confirmed histopathologically were used to establish the diagnosis of LP. A rapid test kit was used for detecting seropositivity for hepatitis B virus (HBV) and hepatitis C virus (HCV). Chi-square test and multivariate regression analysis using SPSS version 16 were used to analyze the collected research data. **Results:** None of the patients of LP in the study group were HCV and HBV positive. None of the control group was positive for both viral infections. In 16 patients (15.68%), the levels of serum aspartate aminotransferase were beyond the normal limits, and higher levels of alanine aminotransferase were detected in 5 patients (4.90%). Bilirubin concentrations higher than the normal limits were detected in total 16 patients (15.68%). **Conclusion:** No association of hepatitis B and C with LP could be established from the present study. More detailed research is needed to establish the correlation between hepatitis B and C and LP.

KEY WORDS: Lichen Planus; Hepatitis B; Hepatitis C

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INTRODUCTION

Lichen planus is a chronic inflammatory skin condition, diagnosed by the characteristic lesions which are pruritic in nature, flat from the top, polygonal in shape, papular having a strikingly violaceous color. Lichen planus (LP) was diagnosed in about 1.2% of all new patients attending the skin clinic of

skin Institute in London over a period of 5 years[1] and 0.38% in India.[2] The overall prevalence of LP is to the tune of <1% in general population. It usually occurs between fourth and fifth decades. No sexual predilection is evident. Skin is the most common site involved in LP though mucosa, nail, and hair involvement can also occur.

The extent and site of involvement are very much related to the natural history of LP. The progress of lichen planus may range from months to years, Altman and Perry showed that spontaneous remission was evident in about two-third patients of LP after a mean duration of 15 months.[3] A prolonged course of the disease was observed in patients having involvement of mucous membrane with or without concomitant skin lesions.

Persistence of residual hyperpigmentation is seen even after the resolution of the skin lesions, but it also shows improvement with time. Malignant changes of affected epithelium particularly of the oral mucosa have been reported.[4] Neoplastic transformation is seen in about 0.3–3.0% cases of oral LP. Other rare associations of LP are scarring alopecia, loss of nails with scarring, and epitheliomata. Considering the above-mentioned complications and incidence of disease, it must be regarded with new concern. The pursuit and discovery of etiological factors, therefore, assume interesting importance.

Much work has been done to find out the etiology of LP, but so far no rational outcome has been achieved. Various factors have been taken into consideration such as genetic, infective, psychogenic, drugs, and autoimmunity.

In recent studies, it has been observed that immunologic involvement has a predominant role in the pathogenesis of LP but has failed to reveal the primary event. Grafting experiments done by Gilhar *et al.* revealed that pathogenesis of LP may be due to migration of cellular elements of immune system and not due to inherent change in the epidermal cells.[5]

Various immunological hypotheses revealed that during the pathogenetic process of LP both CD4+ T and CD8+ T helper cells accumulate in the dermis, whereas CD8+ T helper cells infiltrate the epidermis. It has been postulated that CD8+ cytotoxic T cells identify an antigen which has association with the major histocompatibility complex Class I on keratinocytes present in LP lesions and lyses them.[6-10]

Idiopathic LP has a very strong genetic association. Many familial cases have been reported.[11-14] Familial incidence of around 10.7% was seen in one case series.[10]

Chronic liver diseases like hepatitis C play an subtle role in the pathogenesis of LP, but still association of LP with hepatitis C virus (HCV) infection is questionable. The various associations between HCV and LP could be explained on the basis of geographical locations.

As demonstrated by Lazaro *et al*.,[15] keratinocytes from cutaneous LP lesions are infected by HCV and RNA of this HCV gets translated in these cells as demonstrated by the virus incorporated biopsies of skin lesions.

Though small but significant percentage of HCV infected patients had oral LP as shown by Klanrit *et al*.[16] A replicative form of hepatitis C RNA has been detected in patients having oral LP which is invariably associated with and an immune-mediated destruction of cells in the basal layer. Recently, Pilli *et al*.[17] have demonstrated a link and reassessed the association between cell-mediated immune response against HCV and pathogenesis of LP.

MATERIALS AND METHODS

This study was conducted in the Department of Dermatology, Venereology, and Leprosy at Jawaharlal Nehru Medical College, Ajmer (Central Rajasthan), in year 2016–2017, after approval Ethical Committee of the institute. One hundred two patients of LP were informed about the aim and methodology of the study, and written informed consent was taken beforehand. A detailed history including age, sex, race, residence, clinical symptoms, and their duration was recorded. A total of 100 control subjects were selected from blood donors at blood bank of same institute, who were matching in age and sex to those of study groups. The patients as well as the controls underwent a thorough clinical examination including systemic and cutaneous examination. All cutaneous and mucosal lesions were looked for morphology and sites involved [Figure 1]. Any associated diseases were recorded. Characteristic clinical findings confirmed by histopathological examination of skin biopsy whenever necessary were used to confirm the diagnosis of LP in all the patients.

Immunochromatographic (rapid) test for the qualitative detection of the antibodies specific to HCV in human serum, plasma, or whole blood was used as the test kit. It contains a membrane strip on test band region, which is precoated with recombinant HCV capture antigen (core, NS3, NS4, and NS5).

A rapid test kit was used for hepatitis B virus (HBV) infectivity detection.

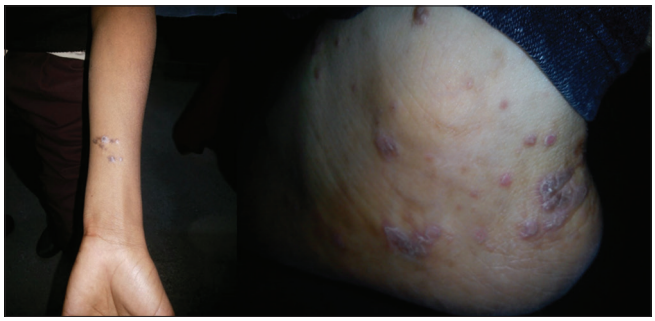

Figure 1: Cutaneous lesions of lichen planus

The collected samples of blood underwent a biochemical analysis for total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) enzymes to rule out any liver injury. The standard normal range used for various liver function tests was ALT from 5 to 40 U/L, AST from 7 to 56 U/L, serum total bilirubin from 0.1 to 1.0 mg/dl, and serum direct bilirubin from 0.1 to 0.4 mg/dl.

Patients between age groups 18 and 65 years and both sexes were eligible to participate. Characteristic clinical findings confirmed by histopathological examination of skin biopsy whenever necessary were used to confirm the diagnosis of LP in all the patients.

Patients who gave written informed consent were included in the study. Clinically doubtful cases, who were also doubtful on histopathological examination and those who refused to sign the consent form were not included in the study.

Two study groups were made named as Group 1 and Group 2. Group 1 consisted of 100 persons who were controls and included blood donors in blood bank, corresponding in age and sex to the second study group. Second study group (Group 2) included 102 LP patients, which were further subdivided as Group 2a (those having involvement of only skin by LP), Group 2b (those having involvement of both skin and mucous membrane by LP), and Group 2c (those having involvement of mucous membrane only).

RESULTS

Out of 102 LP patients, none were HCV and HBV positive. None of the control group was positive for both viral infections. The mean age of the studied patients was 36.73 years ± 12.5 (patients were from ages 16 to 65). Sixty-two patients (60.78%) were male and 40 patients (39.21%) were female. The mean age in females was 34.28 years with standard deviation of 12.4 and in males was 38.32 years with standard deviation of 12.41 [Table 1]. The mean duration of disease was 10.3 months. Maximum patients were in fourth decade (27 patients) followed by second largest number in fifth decade (26 patients). Twenty-one patients had disease in third decade.

Skin alone was the solo site involved in 64 patients (62.74%) of LP, mucous membrane alone in 21 patients (20.58%), both cutaneous and mucous membrane in 16 patients (15.68%), and nails involvement was seen in 5 patients (4.90%). Skin alone involvement was most common presentation followed by mucous membrane alone and both skin and mucous membranes [Table 2].

In 16 patients (15.68%), out of 102 LP patients serum AST levels were more than normal, out of which 8 were in 2a group (3 males and 5 females), 3 were in 2b group (3 males), and 4 were in 2c group (3 males and 1 female). One male patient of nail LP had elevated AST. High levels of ALT were seen in 5 patients (4.90%). Sixteen patients (15.68%) had total bilirubin levels higher than the normal values [Table 3].

In this study, 16 patients had elevated AST levels. Out of 16, a duration of <1 year was seen in 11 patients. Three patients had duration between 1 and 2 years. Two patients had total duration more than 2 years [Table 4].

In this study, out of 102 patients, 16 had elevated serum bilirubin levels of which 7 were in 2a group (6 males and 1 female), 4 were in 2b group (4 males), and 5 were in 2c group (4 males and 1 female) [Table 5].

DISCUSSION

Out of 102 LP patients, none were HCV and HBV positive. None of the control group was positive for both viral infections. Sixteen patients (15.68%) had serum AST levels beyond the normal and increased levels of ALT were seen in 5 patients (4.90%). Sixteen patients (15.68%) had higher levels of total serum bilirubin.

In India, previous studies conducted in New Delhi and Calicut did not show any significant association between LP and HCV, on the other hand, statistically significant association was seen in similar studies conducted in Hyderabad and Bengaluru. A similar case–control study of 104 patients from Kolkata also showed that no association exists between hepatitis C seropositivity and LP.[18]

Various geographical differences may play an important role in the association of LP, and HCV infection, and this association could be well explained by the presence of immunogenic factors such as human leukocyte antigen (HLA)-DR6 allele in some Northern European and Italian patients.

Both cutaneous and mucosal LP have been reported in the past few years especially in the setting of chronic HCV infection.[19] In the acute phase, hepatitis C infection is

Table 1: Age and sex distribution of lichen planus patients

Age (years)	Male	Female
≤20	4	5
21–30	11	10
31–40	19	8
41–50	20	6
51–60	7	8
61–70	1	3
Total	62	40
Mean	38.32	34.28
SD	12.41	12.44

Table 2: Pattern of lichen planus

	Disease pattern			
Number of patient	**Cutaneous+mucosal**	**Cutaneous alone**	**Mucosal alone**	**Nail involvement**
Male	12	33	16	5
Female	4	31	5	0
Total	16	64	21	5

Table 3: Total number of lichen planus patients with elevated liver function test (AST)

Subgroup	Total number of LP with elevated LFT	Male	Female
IIa	8	3	5
IIb	3	3	0
IIc	4	3	1
Nail LP	1	1	0

IIa: LP with cutaneous lesions only, IIb: LP with both cutaneous and mucosal lesions, IIc: LP with mucosal lesions only. LP: Lichen planus, AST: Aspartate aminotransferase, LFT: Liver function test

Table 4: Relation of elevated LFT with duration of LP

Duration of illness (years)	Abnormal LFT (AST)		
	Female	Male	Total
Up to 1 year	5	6	11
1–2 years	Nil	3	3
>2 years	1	1	2
Total	6	10	16

LP: Lichen planus, AST: Aspartate aminotransferase, LFT: Liver function test

Table 5: Relation of elevated serum bilirubin level with the type of LP

Subgroup	Abnormal serum bilirubin		
	Female	Male	Total
IIa	1	6	7
IIb	0	4	4
IIc	1	4	5

IIa: LP with cutaneous lesions only, IIb: LP with both cutaneous and mucosal lesions, IIc: LP with mucosal lesions only. LP: Lichen planus

usually asymptomatic and does not show any specific disease manifestations; thus, it is seldom recognized and largely remains undiagnosed, which eventually leads to chronic conditions of hepatitis C.[20] However, there remain wide geographical variations in the prevalence of hepatitis C infection in patients with LP, which varies from 0% in England[21] to 63% in Japan.[22]

HCV virus is categorized as a single-stranded RNA virus. The main routes of its transmission are through blood and its products. The various proposed mechanisms for the pathogenesis of LP are as follows:

1. HCV virus has the unique capability of cytopathic replication in various cell types outside the liver.[23]
2. HCV triggers an auto-immune process which targets antigens expressed on extra-hepatic cells.[24] It is proposed that HCV may mimic a structural component of the keratinocyte, which leads to production of autoantibodies.[25]
3. Immune complexes with antibodies are formed as a result of persistent infection. These complexes get deposited on small blood vessels.
4. Activated CD8 T helper cells, various cytokines, and expansion of specific B cell clones are the triggers for immunological process which eventually leads to dermatological manifestations of the disease.[24,26]

HCV could be a potential antigen presented by Langerhans cells, leading to activation and migration of lymphocytes, which in turn damages the basal cells through various cytokines produced by cytotoxic T cells.[27] Carrozzo *et al*. have postulated that genetic polymorphism of interferon-gamma and tumor necrosis factor-alpha may play an important role in the pathogenesis of oral and orocutaneous involvement in LP.[28]

Whether HCV induces the pathogenesis of oral lichen is still uncertain, but a couple of hypotheses have suggested the mechanism by which oral LP is triggered by HCV. The first hypothesis proposed that replication of HCV is linked with the oral epithelium and thus it directly contributes to the formation of oral LP lesions. The second hypothesis suggested that the repeated activation of immune cells occurs as a result of extremely high mutation rates of HCV virus; thus, the possibility of cross-reaction with its own tissue gets increased subsequently the risk of autoimmune disease also gets increased. Cross-reactivity leading to activation of various immune cells against epithelial cells is favored in some genotypes.[25] A group of researchers has proposed that HCV infection does not directly contribute to the pathogenesis of oral LP because multiplication of HCV was seen in mucosa both with and without oral LP. In addition to, this a infiltrate of mononuclear cells was seen around the epithelial cells of patients who were seropositive for hepatitis C with and without oral LP. However, the researchers of this study did not rule out the possibility of changes induced in the host by HCV that might have triggered an autoimmune response.[29]

The control populations had significant lower levels of HCV antibodies whereas the prevalence of similar antibodies was much higher in patients having cutaneous and mucosal LP (non-LP dermatological patients or population of blood

donors) in Germany,[30] Italy,[31] Spain,[32] USA,[33] and Japan[19] suggesting an etiologic role for HCV in pathogenesis of LP. In contrast, the studies in France[34,35] and England[21,36] were not able to demonstrate a statistically significant association between hepatitis C virus and LP.

In India, studies conducted in New Delhi and Calicut failed to demonstrate a statistically significant association between hepatitis C and LP. On the contrary studies conducted in Hyderabad and Bengaluru have shown a significant association.

The aim of the present study was to examine the status of hepatitis C in patients and controls of LP. Any association between the two entities could not be established because none of the patients nor the controls having LP were seropositive for hepatitis C. This lack of association between the two entities was also seen in some other similar studies as well.[21,37] No definite association between LP and chronic hepatitis C was observed in a study conducted by Michele *et al*. They proposed that frequency of each disease in the population groups may be the determining factor for any possible association between the two entities, which further explains the wide geographic variations seen in these diseases.[38] However, some studies as conducted by del Olmo *et al.* stated that HCV plays an important role in the pathogenesis of chronic liver diseases observed in patients with oral LP and that treatment of the disease with interferon-α, which acts by inhibiting virus multiplication, may result in development of a lichenoid reaction to this drug.[39]

Sequences of HCV have been found in the serum of patients with oral LP, and this supports the association between hepatitis C seropositivity and oral LP, and seldom it was seen that HCV was able to replicate in tissues of oral LP and this may a possible factor which plays an important role in pathogenesis of damage occurring in the mucosal layers.[31,40] RNA genome of HCV is single-stranded and it uses the negative strand as a template in the infected tissues to replicate. Hence, the single-stranded negative-strand RNA presents in the infected tissues is considered as a marker of HCV replication. Furthermore, recent data show that the HCV specific T-cells can be seen in the oral mucosal layers of patients with chronic HCV and oral LP.[17]

Various literature available on MEDLINE search has shown an association between LP and HCV infection. If at all this is a true association, than LP in certain population groups can be used as a marker of HCV infection in patients who are asymptomatic, which may lead to early diagnosis and treatment of the disease and eventually a better prognosis. Early identification of extra-hepatic manifestations of HCV infection plays an important role in ongoing patient care. If this is not a true association, then routine examinations and tests of patients with oral lichen planus for HCV may unnecessarily add up to the medical cost and wastage of resources, increased anxiety, and increased cost of therapy among those tested may be other harmful effects. Hence, it is important to establish that is there any association exists between LP and HCV infection so that proper guidelines regarding the routine serology testing of HCV patients with LP may be detailed to clinicians. In this present study, no definitive relationship between hepatic disease and LP could be established.

In the present study, we could not find any association of LP with HCV and HBV infection. However, there were 16 patients (15.68%) who had elevated serum bilirubin levels and AST levels in the patient group, which does not correlate with disease duration and specific site of involvement.

Geographical factors are partly responsible for the association of LP with hepatitis C infection and liver disease. It has been postulated that the variations observed in the association of LP and HCV with respect to the geographical location can be explained by the different genetic factors which control the immune responses of the host. HLA Class II allele HLA-DR6 is believed to be linked with HCV-related LP, and this might be a good explanation of the peculiar geographical heterogeneity of the association between HCV and LP. Presently, available literature is not enough to determine whether there is any role of HCV in the pathogenesis of LP.

The use of various methods poses a hurdle in the comparison of results. The published results are also directly affected by the inclusion and exclusion criteria used to select the patients. Thus, disagreements observed between various studies conducted till now can be explained by the varied geographical distribution of hepatitis C infection among different countries, a bias in the selection of the population for the study and, last but not least, is the genetic predisposition to immune hyper-responsiveness. There have been many paradoxical and inconsistent reports regarding this association; still the present Indian literature points that LP patients do not have an increased incidence of liver disease or evidence of hepatitis B or hepatitis C or any other chronic liver ailment. To conclude, the findings of the present study cannot establish an epidemiological or causative link between LP and HCV in population of central Rajasthan.

The main limitation of this study was a smaller sample size. Furthermore, multicenter studies with a big sample size are required to establish the connection between LP and chronic hepatitis.

CONCLUSION

The outcomes from this study did not show any reciprocity between liver disease and LP, and further comprehensive studies with a bigger sample size are required to establish the association between HCV and LP.

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