LICHEN PLANUS AND LIVER DISEASE

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One hundred and twenty consecutive, fresh patients with lichen planus were studied for liver function abnormalities. Patients with obvious immunological disorders and other diseases associated with liver dysfunction and those with factors liable to cause liver injury or produce lichenoid drug eruptions were excluded. Seventy-five patients with benign dematological disorders acting as controls were similarly studied. Levels of serum bilirubin, SGOT and SGPT were not significantly (more than twice) elevated in either the patients or controls. Only one patient had elevated levels of serum alkaline phosphatase. Altered levels of serum proteins were observed in 80 (66.0%) patients and 48 (64.0%) controls, the difference being statistically insignificant. HBs Ag detection was done in 75 out of 120 patients with lichen planus, of whom 7 (9.3%) tested positive. All the 11 (9.2%) patients with hepatomegaly were negative for HBs Ag. In these patients with hepatomegaly all liver function parameters were within normal range except total serum proteins which were elevated in 4 with reversal of A/G ratio in only 2. Our study did not show any increased incidence of clinical or biochemical evidence of liver disease in patients with lichen planus.

Key words : Lichen planus, Chronic liver disease, Liver function abnormalities

Introduction

The cause of lichen planus (LP) remains a mystery despite indications linking this eruption with associated conditions like ulcerative colitis,[1] myasthenia gravis[1] and alopecia areata,[1] and hypogammaglobulinemia.[2] Several recent reports have raised the possibility that a relationship exists between LP and liver disease.[3]

LP was initially reported in cases of primary biliary cirrhosis (PBC) on Depenicillamine therapy.[4] Workers from Italy reported a startling figure of 13.5% of LP patients having chronic active hepatitis (CAH).[5] This strong association which was strengthened by similar Spanish[6] and American[7] studies, was not confirmed by other investigators from Sweden,[8] the United Kingdom,[9] and the United States.[10] The largest study conducted by the Italian group of Epidemiologic Studies in Dermatology (GISED)[11] on 577 LP patients and 1008 controls, provided epidemiologic evidence of the relationship of LP and liver disease.

Considering the controversy surrounding LP and liver disease, and the extreme variation in the observations of different series from various geographical populations, we carried out investigations on a group of patients with LP from a North Indian City, and compared the historical, physical and laboratory findings with a group of controls.

Materials and Methods

One hundred and twenty untreated patients (62 males, 58 females) with LP (either cutaneous or mucosal or both), attending the Dermatology out patient department of our hospital, were accepted for the study. Their mean age was 38.2 years (range 11 to 76 years). Seventy-one (59.2%) had cutaneous LP alone, among those with oral LP, 8 (16.3%) had erosive lichen planus. Patients with obvious co-existing immunological disorders, those with other diseases associated with liver dysfunction (e.g. porphyria) and those with a history of chronic alcohol intake or on prolonged drug treatment known to cause either

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lichenoid lesions or liver damage were excluded from the study.

An informed consent was taken from all patients and were evaluated for (i) any known history of liver disease including blood transfusion, (ii) a thorough general physical work-up, (iii) liver function abnormalities which included serum levels of liver enzymes (SGOT, SGPT and alkaline phosphatase), bilirubin and proteins, and (iv) the presence of hepatitis B surface antigen. Investigations were repeated after one week to eliminate any laboratory errors or chance findings. Seventy-five patients with benign, non immunological dermatological disorders and without any known liver dysfunction acted as controls.

The criteria used for diagnosing common liver disorders reportedly associated with LP were- (a) Chronic Active Hepatitis (CAH) : Serum glutamate oxaloacetate transaminase (SGOT) greater than 10 times normal or serum glutamate pyruvate transaminase (SGPT) greater than 5 times normal plus a doubling of serum globulin levels and evidence of CAH on liver biopsy in a patient in whom there has been documentation of liver disease for longer than 6 months (Mayo Clinic Criteria).[19] (b) Primary Biliary Cirrhosis (PBS) : Two to five fold elevation of serum alkaline phosphatase supported by a positive anti-mitochondria antibody test.[12]

In assessing serum enzymes, values were considered to be significantly abnormal only if the levels were elevated to more than twice the upper limit of normal values in both samples, taken one week apart. Serological markers for HBsAg were assessed by ELISA (Abbot, USA). The chi-square test was employed to determine whether the incidence of liver function test abnormalities among the cases and controls was statistically significant.

Results

Nine (7.5%) patients had past history of jaundice, 4 (3.3%) had a history of blood transfusion and 1 (0.8%) patient gave history of acute viral hepatitis in the past. No patients had any history of bleeding, pedal oedema, ascites, or encephalopathy. Four (5.3%) controls had past history of jaundice and 2 (2.7%) had history of blood transfusion.

General physical examination

This was normal in all the patients except for the presence of hepatomegaly in 11 (9.2%). The liver was soft to firm, non-tender and palpable for upto 4 cm below the right costal margin. Splenomegaly was observed in 2 (1.7%) cases, while ascites and oedema were not noted in any patient. There was no evidence of clinical jaundice in any of the patients.Among the controls, other than soft hepatomegaly in 6 (8%) no other positive findings were observed.

Liver function tests

Levels of serum bilirubin, SGOT and SGPT were not significantly elevated (more than two times) in either the patients or controls. Only 1 patient had elevated serum alkaline phosphatase. Altered (decreased or increased) levels of serum proteins were observed in 80 (66.7%) patients and 48 (64.0%) controls, the difference being statistically insignificant. Similarly though albumin and globulin levels were altered in 9 and 31 patients respectively, the differences were not statistically significant as compared to controls. The mean values of the various tests are shown in Table I. None of the patietns with altered albumin globulin ratio had any clinical or sonographic evidence of cirrhosis liver.

Hepatitis B surface antigen

Tests for the detection of the hepatitis B surface antigen were performed in 75 of the 120 LP patients, of whom 7 (9.3%) tested positive. None of these patients, however had a history of blood transfusion nor could they recollect any episode of jaundice in the past. None of the controls tested was positive for the same.

LFT and HBsAg in LP patients with hepatomegaly

Of the 120 patients, 11 (9.2%) had hepatomegaly. All of them were negative for the HBsAg. Liver function tests

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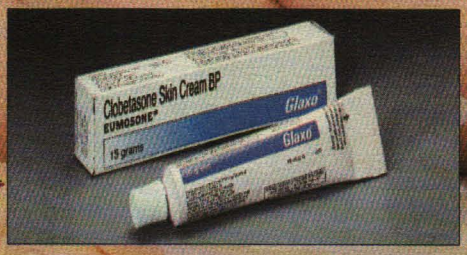

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were also within normal range in all patients except total proteins which were elevated in four. Two out of these 4 showed reversal of A/G ratio.

LFTs in HBsAg positive patients

Table.I. LFTs in patients with LP and controls

Liver Function Tests	LP cases	Controls	P value
(normal values)	(n=120)	(n=75)	
Serum bilirubin (upto 0.8 mg/dl)	0.8±0.2 (Range 0.3 to 1.6)	0.7±0.2 (Range 0.2 to 1.5)	NS
SGOT i.u (0-20 i.u.)	14.6±6.9 (Range 4 to 37)	13.1±4.8 (Range 5 to 32)	NS
SGPT i.u. (0-15 i.u)	11.5± 6.6 (Range 4 to 46)	10.6±3.9 (Range 4 to 26)	NS
Alkaline phosphatase (K.A.U.)	12.8±15.0 (Range 4 to 138)	10.6±4.1 (Range 3 to 5)	NS
Serum albumin (3.5-5.5 g/dl)	3.2±0.01 (Range 3 to 6.2)	3.2 ± 0.01 (Range 6 to 25)	NS
Serum globulin (2-3 g/dl)	3.3±0.7 (Range 1.7 to 5.3)	3.3±0.5 (Range 1.6 to 4.6)	NS
Total serum protein (5.5-7 g/dl)	7.7±3.8 (Range 6 to 9.8)	7.9±3.6 (Range 6.2 to 9.2)	NS

None of the 7 (9.3%) patients tested positive for HBsAg had hepatomegaly. Serum bilirubin and serum enzymes were normal in all the 7 patients, however, 6 of them had increased total serum proteins, and the A/G ratio was reversed in 3 patients.

Discussion

Although the pathogenesis of LP still remains unknown, abnormalities in both humoral and cellular immune mechanisms may play an important role.[13,15] Similar mechanisms may be involved in the pathogenesis of certain liver disorders as well. Lenkei et al[16] have reported that antibodies to the basal cells of all keratin producing epithelia were frequent in patients with chronic hepatitis B. Metaplasia of infected hepatocytes could lead to the expression of a common antigen in hepatocytes and keratinocytes which would explain the association of the two diseases as reported in some studies.

In fact, Rongioletti and Rebora[17] and Rebora et a[15] reported a high prevalence (11.3% to 13.5%) of CAH in their LP patients. Such an impressive prevalence, the histologic and immunologic similarities between the two diseases led them to support the view that the LP-CAH association was not fortuitous and that both diseases may have the same immunopathogenesis. Their studies, however, have had to face criticism of selection bias which probably overestimated the true prevalence of liver disease, as well as the absence of controls to confirm an increased prevalence of liver disease in LP. Similarly no clearly defined disease criteria were mentioned in another Italian study which had shown an increased association of LP and liver disease.[11]

Most abnormalities observed in our study were small increase in the levels of single enzyme level and there was no unequivocal biochemical evidence of liver disease in any of 120 patients with LP. This observation is also supported by various other workers[8,18] who were unable to confirm the association of LP with liver disease and did not feel that LP patients should be routinely screened for liver disease. However, there is an important difference between these studies due to the different time schedules employed. While those reporting a positive association[5,17] studied the occurrence of CAH in the time period that elapsed between the initial diagnosis of LP and the subsequent follow-up (which ranged from 8-180 months from the LP diagnosis), those reporting negatively[8] by contrast, studied the actual condition of freshly diagnosed LP patients had been present for a variable period of upto 7 years, and no liver disease had yet developed in any of our patients. Besides, the high prevalence of liver disease reported in the Italian studies could be due to the high prevalence of HBsAg poitivity in the Italian population at large as compared to the prevalence from other geographical regions (34% in Genoa, Italy as compared to 0.1% in London).[9] Although liver biopsy is the final investigation to give the true incidence of liver disease there would be little justification in doing it, even in pa-

tients with two times raised transaminases, since for the diagnosis of CAH, one needs to have at least 5 times rise in them, which none of our patients had.

The findings of HBsAg in higher proportion of our patients need some reflection. The prevalence of HBsAg positivity in India varies from 2.5% to 5% and the slightly higher frequency (9.3%) in our study is very difficult to explain. Although this is likely to be a chance finding, it cannot be totally ignored either, since a high percentage of positivity of HBsAg has been reported in LP patients. Rebora et al [19] found a higher than expected prevalence of anti HBV and anti HCV antibodies in LP patients with chronic liver disease as compared to the general Italian population and felt that their results were in good agreement with the increase of HBsAg positivity noted in GISED study.[11]

Thus our study does not show an increased incidence of clinical or biochemical evidence of liver function abnormalities in patients with lichen planus. Strict exclusion criteria employed in our study may explain the negative association between LP and chronic liver disease. Thus an extensive search for an underlying liver disease is unwarranted in our context. To know the true incidence of liver disease in LP one may have to study a larger number of patients, do more sensitive liver function tests and observe these patients over a prolonged period. The controversy surrounding the association between LP and liver disease is nevertheless fascinating.

References

1. Tan RSH. Ulcerative colitis, myasthenia gravis, atypical lichen planus, alopecia areata, vitiligo. Pro R Soc Med 1974; 67:195-196.

2. Mann RJ, Wallington TB, Warin RP. Lichen planus with late onset hypogammaglobulinemia : a casual relationship? Br J Dermatol 1982; 106:357-360.

3. Parsons ME, Russo G, Millikan LE. Dematologic disorders associated with viral hepatitis infections. Int J Dermatol 1996; 35:77-81.

4. Seehafer JR, Rogers RS, Flaming CR, et al. Lichen planus - like lesions caused by penicillamine in primary biliary cirrhosis. Arch Dermatol 1981; 117:140-142.

5. Rebora A, Rongioletti F, Canepa A. Chronic active hepatitis and lichen planus. Acta Derm Venereol (Stockh) 1982; 62: 351-352.

6. Olmo JA del, Bagan JV, Rodrigo JM, et al. Oral lichen planus and hepatic cirrhosis. Ann Intern Med 1989; 110: 666.

7. Korkji W, Chaung TY, Soltani K. Liver abnormalities in patients with lichen planus. A retrospective case control study. J Am Acad Dermatol 1984; 11: 609-615.

8. Mobaken H, Nilsson LA, Olsson R, et al. Incidence of liver disease in chronic lichen planus of the mouth. Acta Derm Venereol (Stockh) 1984; 64: 70-73.

9. Monk B. Lichen planus and the liver. J Am Acad Dermatol 1985; 12:122-124.

10. Powell FC, Dickson ER, Rogers RS III. Lichen planus and chronic active hepatitis. J Am Acad Dermatol 1984; 10 : 841.

11. Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED). Lichen planus and liver diseases: a multicentre case control study. Br Med J 1990; 300:227-230.

12. Maddrey WC. Chronic hepatitis. In: Zakim D and Boyer TD, eds. Hepatology. A Textbook of Liver Disease. 2nd edn. Vol II. Philadelphia: W.B.

13. Olsen RG, Du Plesis DP, Barcon C, et al. Lichen planus dermopathy: Demonstration of a lichen planus specific epidermal antigen in affected patients. J Clin Lab Immunol 1983; 10: 103-106.

14. Bhan AK, Harrist TJ, Murphy GJ, et al. T-cell subsets and Langerhans cells in lichen planus : In situ characterisation using monoclonal antibodies. Br J Dermatol 1981; 105: 617-622.

15. Gionotti B, De Panfilis G, Manara GC, et al. Macrophage - T - lymphocyte interaction in lichen planus.An electron microscopic and immunocytochemical study. Arch Dermatol Res 1983; 275: 35-40.

16. Lenkai R, Biberfeld G, Buligescu L, et al. Auto antibodies against the basal cell layer: an association with chronic hepatitis B. Clin Immunol Immunopathol 1983; 26: 436-441.

17. Rongioletti F, Reobora A. Chronic active hepatitis and lichen planus. A retrospective survey. Acta Derm Venereol (Stockh) 1984; 64: 52-56.

18. Scully C, Potts J, Mamburger J, et al. Lichen planus and liver disease: how strong is the association? J Oral Pathol 1984; 14: 224-226.

19. Rebora A, Robert E, Rongioletti F. Clinical and laboratory presentation of lichen planus patients with chronic liver disease. J Dermatol Sci 1992; 4: 38-41.

20. Virgili A, Robert E, Rebora A. Hepatocellular carcinoma and lichen planus: Report of two cases. Dermatology 1992; 184: 137-138.