Lichen planus and Chronic Active Hepatitis

A Retrospective Survey

ALFREDO REBORA and FRANCO RONGIOLETTI

Department of Dermatology, University of Genoa, Genoa, Italy

Rebora A, Rongioletti F. Lichen planus and chronic active hepatitis. A retrospective survey. Acta Derm Venereol (Stockh) 1984; 64: 52–56.

In a retrospective survey 95 in-patients with non erosive lichen planus (LP) were summoned to be investigated by means of routine liver tests. 44 patients responded. Remarkable abnormalities of liver tests were found in 6 patients who were further studied for antibodies to smooth muscle and mitochondria and submitted to liver biopsy. Histological diagnosis revealed chronic active hepatitis (CAH) in 5 cases (11.3%). Such an impressive prevalence and the histologic and immunologic similarities between the two diseases support the view that the association LP-CAH is not fortuitous and that both diseases may have the same autoimmune pathogenesis. Accordingly LP may be regarded as a major risk factor for liver cirrhosis. *Key words: Liver cirrhosis; Autoimmunity.* (Received April 23, 1983.)

A. Rebora, Department of Dermatology, University of Genoa, V.le Benedetto XV, 7 Genoa, Italy.

In a previous communication (1) one of us reported patients associating erosive lichen planus (LP) with a severe liver disease mostly with the features of chronic active hepatitis (CAH). Successively another patient has been described associating the same skin disease with CAH (2) and in a retrospective study (3) some 13.5% of patients with non-erosive LP proved to have CAH at the time of examination or developed it in the following years.

We report the results of the extension of the study confirming that LP is associated with CAH with exceeding frequency.

PATIENTS AND METHODS

Over the period 1954–80 ninety-five in-patients entered our clinic with non erosive-LP and only 37 had been sufficiently investigated for liver function.

All 95 patients were summoned to be re-investigated and eventually liver biopsied; 44 patients responded and 35 did not. 16 had died in the meantime.

Of the 35 patients who did not respond, 5 (14%) had had some abnormality in their liver tests; one of them had had liver cirrhosis as revealed by sonography. Of the 44 respondents, 10 (22.7%) had had some abnormal liver tests.

In the 44 respondents, SGOT and SGPT, alkaline phosphatase (APh), gammaglutamyl transpeptidase (GT), serum electrophoresis, immunoelectrophoresis, bilirubinemia, hepatitis B markers, antinuclear, anti-smooth muscle (SMA) and anti-mitochondria (AMA) autoantibodies, LDH, pseudocholinesterase, prothrombinemia, fibrinogenemia and sideremia were then studied.

RESULTS

Of the 44 respondents, 20 patients were found to have no abnormality in their tests; 18 had some of them impaired; in particular: GT was altered in 6 patients, SGOT and SGPT in 5, APh in 2, gamma-globulines in 7, IgG in 4, IgM in 4; bilirubinemia was normal in all cases.

Six patients had laboratory evidence suggesting liver biopsy, that revealed CAH in 5 cases (11.3%) (Table I).

All of the CAH patients were HBs Ag negative, but two were anti-HBs and anti-HBc positive and one was anti-HBc and anti-HBe positive.

None of them had a history of alcoholism nor did anyone report taking liver toxic drugs.

A mean of 85 months had elapsed between the initial diagnosis of LP and liver biopsy. Cases 1 and 2, in whom 144 and 84 months respectively had elapsed, belonged to the group which originally had normal liver tests. Case 3, 180 months, had been poorly studied at the time of his first examination when cases 4 and 5 (6 and 11 months) had liver tests already impaired (Table I).

Among the causes of death of the deceased patients one case of ante-mortem bioptic diagnosis of CAH (6%) was discovered. Another patient had died in hepatic coma but autopsy had not been performed (Table II).

DISCUSSION

The global prevalence of chronic hepatitis/cirrhosis in our geographic area is around 0.25–0.5% (4). We reductively considered only a small proportion of putative CAH-patients, for ethical reasons excluding from the liver biopsy patients with modest laboratory evidence of liver disease, who may have had CAH as well.

Yet, CAH was proved in an impressive 11.3% of LP patients.

It is unlikely that only patients with actual symptoms of liver disorder responded to our summon. In fact, 14% of the non-respondents and 23% of the respondents had some defective liver tests before being re-investigated and such difference was statistically non significant ($\chi^2=0.903$; $p>0.05$).

A visceral involvement has seldom been reported in LP: myasthenia gravis, thymoma, ulcerative colitis, polymyositis, malignant lymphoma have been described.

CAH is a chronic inflammatory and fibrosing liver disease of varied etiology with multisystem involvement and immunologic disturbance. It may be associated with other

Table I. *Laboratory and histological findings in the six lichen planus patients submitted to liver biopsy*

SGOT and SGPT = transaminases; APh = alkaline phosphatase; GT = gamma-glutamyl transpeptidase; BIL = bilirubin; G = gamma globulins %; ANA = antinuclear antibodies; SMA = antismooth-muscle antibody; AMA = antimitochondrial antibody

Case ...	1	2	3	4	5	6	
Sex ...	m	m	m	f	f	m	Normal
Age ...	26	55	61	53	65	44	Values
SGOT	87	94	30	43	144	45	15–45
SGPT	240	90	56	60	183	67	15–45
APh	150	120	240	265	250	94	70–210
GT	52	51	19	60	71	73	5–25
BIL	0.4	0.7	1.0	0.3	0.8	0.9	0.3–1.2
G	22.5	17	23	32.9	22.5	17.9	19–21%
IgG	2 300	1 423	1 925	2 876	2 334	2 130	800–1 500
IgM	175	98	45	158	95	210	80–170
ANA (1/10)	+ Nucleolar, + speckled	Neg.	Neg.	+ Homogeneous	+ Homogeneous	Neg.	
SMA (1/10)	Neg.	+	Neg.	+	+	Neg.	
AMA (1/10)	Neg.	Neg.	Neg.	Neg.	+	Neg.	
Histopathology	CAH	CAH	CAH	CAH	CAH, initial cirrhosis	Steatosis, slight portal infiltration	
Interval (months)[a]	144	84	180	6	11	–	

[a] Interval between diagnosis of LP and diagnosis of CAH.

disorders with immunologic basis such as ulcerative colitis, rheumatoid arthritis, fibrosing alveolitis, sicca syndrome, polymyositis, Hashimoto's thyroiditis, haemolytic anemia, etc.

Cirrhosis may be observed on liver biopsy, but the typical histopathologic lesion is a heavy lymphocytic infiltrate of the portal tracts which penetrates and disorganizes the parenchyma.

Skin symptoms are reported as mild but persistent jaundice, spider naevi, palmar erythema and purpura, but LP has never been included.

To our knowledge only two cases of non erosive LP have been associated with CAH (5, 6), but in both cases the authors considered the association as being only fortuitous.

Yet, histologic and immunologic similarities between LP and CAH are obvious.

In both diseases, the lymphocyte infiltrate obscures the first line of parenchymal cells (Figs. 1, 2), colloid bodies can be found and a fibro-sclerotic healing process may take place. These histologic aspects resemble the graft-vs.-host reaction (7); in fact, liver grafts display similar changes when rejected (8) and a lichenoid skin eruption may occur after bone marrow transplantation (7).

An autoimmune mechanism had been suggested in both diseases that, in fact, may be found to be associated with other autoimmune disorders. In addition to the afore-mentioned ones, LP has been observed combined with alopecia areata, vitiligo and bullous pemphigoid.

Humoral immunity is largely involved in both diseases. In LP, globular IgM, complement and fibrin deposits may be observed at the basal zone, in the upper dermis and around hair follicles. Hypergammaglobulinemia and high levels of IgG are common serologic findings in CAH; circulating ANA and SMA, positive LE cell preparations and rheumatoid factor are found in a high proportion of CAH patients (9). Antibodies to antigens of the hepatocyte surface membrane have been proved to circulate in CAH (10) and IgG to bind in vivo to the surface of CAH hepatocytes (11).

In both diseases, however, the cell-mediated immunity is likely to be primitively committed. First of all, both CAH and LP have been found in patients with hypo- and agammaglobulinemia (12, 13); lymphocytes in the LP infiltrate are almost exclusively T-cells (14) and T-cells from patients with CAH are cytotoxic to liver cells in tissue culture

Table II. *Causes of death of the sixteen deceased lichen planus patients*

	Sex	Age	Causes of death
1	f	61	Cirrhosis, bronchopneumonia, heart failure (ante-mortem bioptic CAH)
2	f	74	Hepatic coma
3	m	57	Ictus cerebri
4	m	70	Colonic cancer in ulcerative colitis
5	f	70	Breast cancer, diabetes
6	f	85	Heart failure
7	f	88	Bladder cancer
8	m	51	Multiple sclerosis
9	m	39	Heart failure, diabetes
10	m	73	Myocardial infarction
11	m	69	Bladder cancer
12	m	74	Lung cancer, diabetes
13	m	80	Heart failure
14	m	65	Heart failure, diabetes
15	f	67	Ictus cerebri
16	f	81	Ictus cerebri

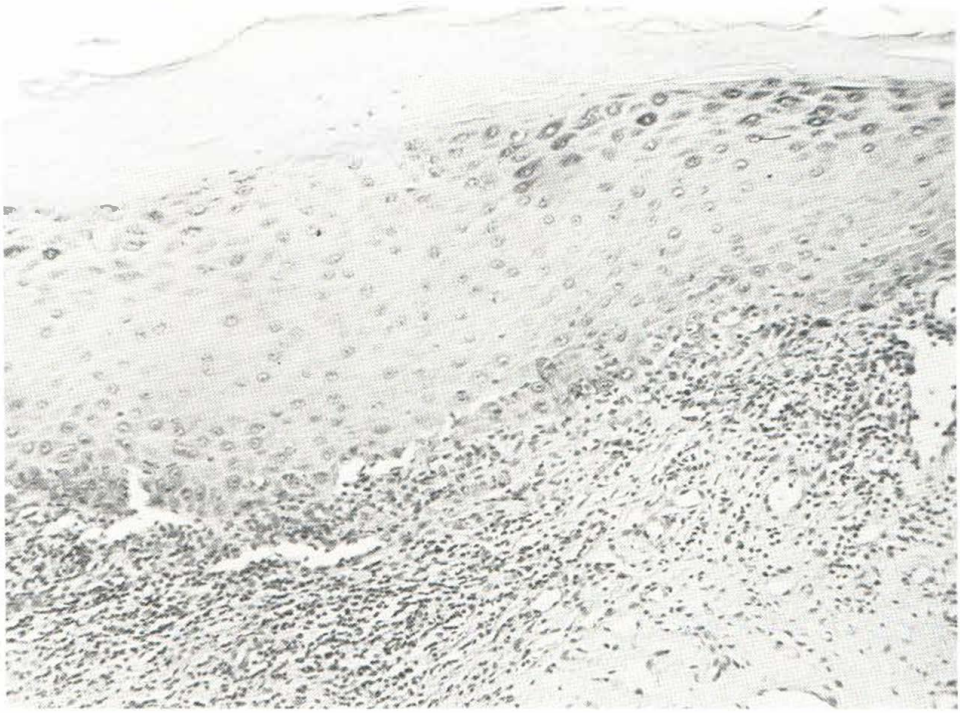

Fig. 1. A lymphocytic, band-like subepidermal infiltrate obscures the basal layer and invades the epidermis.

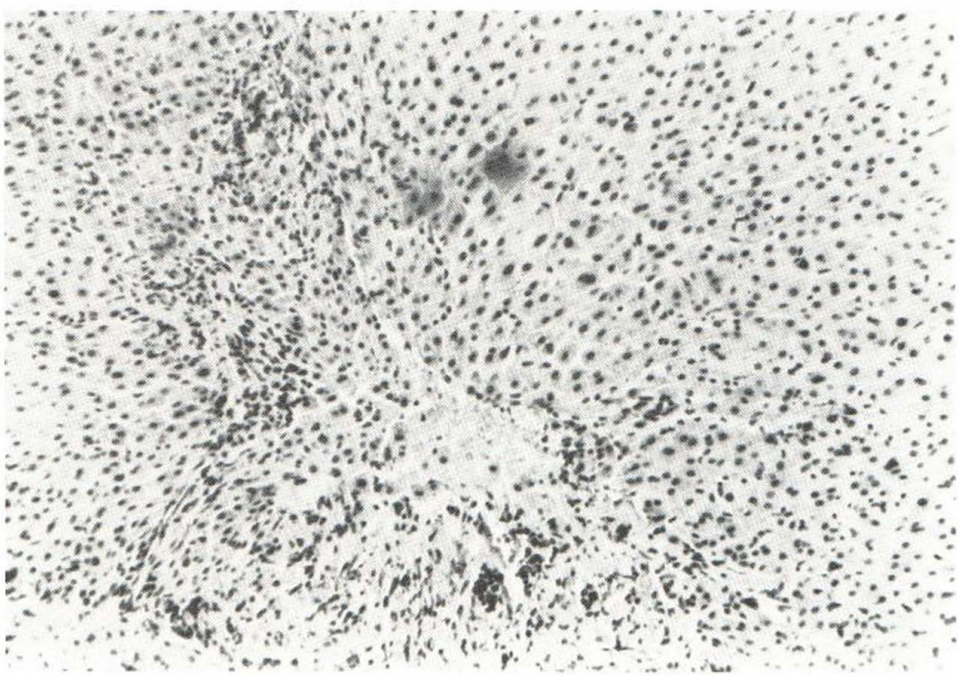

Fig. 2. A lymphocytic infiltrate obscures the first line of hepatocytes (lamina limitans) and disorganizes the hepatic lobule.

(8). Finally, both diseases have been assimilated to the graft-vs.host reaction, a well known T-cell-dependent phenomenon.

Recently, Graham-Brown et al. published an anedoctal report of five LP patients with primary biliary cirrhosis (PBC) (15).

PBC is a chronic cholestatic liver disease, rare in Southern Europe (16), primarily involving bile ducts and presenting with jaundice and pruritus. There are also asymptomatic cases in which the diagnosis is based only on high titres of AMA and on liver biopsy (17).

In initial cases, however, histopathology cannot distinguish PBC from CAH(18) and some CAH-patients are both SMA and AMA-positive. In addition AMA have been shown to be heterologous and only their M2 fraction is said to be PBC-specific (19).

PBC seems to prevail in LP patients of Northern Europe and CAH in Southern Europe cases, but, in fact, both diseases may associate with LP. The erosive quality of the mucosal lesions in LP is an indication of the particular aggressiveness of the morbid process and should be regarded as a major risk factor of liver cirrhosis.

REFERENCES

1. Rebora A. Lichen planus and the liver. Lancet 1981; ii: 805–806.
2. Monk BE, Pembroke AC. Skin problems in chronic active hepatitis. Lancet 1981; ii: 1045.
3. Rebora A, Rongioletti F, Canepa A. Chronic hepatitis and lichen planus. Acta Derm Venereol (Stockh) 1982; 62: 351–352.
4. MacKay IR. Chronic hepatitis disease: prevalence postulates and prevention. In: Bartoli E, Chiandussi L, Sherlock S, eds. Systemic effects of HBsAg immune complexes. Padova, Piccin, 1981: 300–308.
5. Calandra P. Lichen ruber planus, morfea, sclerosi sistemica ed epatite cronica attiva. G Ital Derm Vener 1972; 47: 436–439.
6. Binet D, Girard J, Avram A, Hemast M., Blav N, Aron-Brunetière R. Hépatite chronique active et lichen planus. Journées Dermatologiques de Paris 1979; p. 86.
7. Saurat JH, Gluckman E. Lichen planus like eruption following bone marrow transplantation: a manifestation of the graft-vs.-host disease. Clin Exp Dermatol 1977; 2: 335–344.
8. Paronetto F, Vernace SJ. Immunological studies in patients with chronic active hepatitis. Cytotoxic activity of lymphocytes to autochthonous liver cells grown in tissue culture. Clin Exp Immunol 1975; 19: 99–104.
9. Eade O, Wright R. Liver disease. In: Holborow EJ, Reeves WG, eds. Immunology in medicine. New York: Acad Press; London: Grune & Stratton, 1977: 662–664.
10. Jensen DM, McFarlane IG, Portmann BS, Eddleston ALWF, Williams R. Detection of antibodies directed against a liver specific membrane lipoprotein in patients with acute and chronic active hepatitis. N Engl J Med 1978; 299: 1–7.
11. Hopf V, Arnold W, Meyer zum Büschenfelde KH, Forster E, Bolte JP. Studies on the pathogenesis of chronic inflammatory liver disease. 1. Membrane fixed IgG on isolated hepatocytes from patients. Clin Exp Immunol 1975; 22: 1–8.
12. Tan RSH, Samman PD. Thymoma, acquired hypogammaglobulinemia, lichen planus, alopecia areata. Proc R Soc Med 1974; 67: 196–197.
13. Good RA, Page AR. Fatal complication of virus hepatitis in two patients with agammaglobulinemia. Am J Med 1960; 29: 804–810.
14. Bhan AK, Harrist TJ, Murphy GF, Mihm MC Jr. T cell subsets and Langerhans cells in lichen planus: in situ characterization using monoclonal antibodies. Br J Dermatol 1981; 105: 617–622.
15. Graham-Brown RAC, Sarkany I, Sherlock S. Lichen planus and primary biliary cirrhosis. Br J Dermatol 1982; 106: 699–703.
16. Eddleston ALWF. Immunology and the liver: In: Parker CW, ed. Immunology. Philadelphia: WB Saunders Company, 1980: 1009–1050.
17. James O, Macklon AF, Watson AJ. Primary biliary cirrhosis. A revised clinical spectrum. Lancet 1981; i: 1278–1281.
18. Sheuer PJ. Liver biopsy in chronic hepatitis. 1968–78. Gut 1978; 19: 554–557.
19. Berg PA, Holmberg JC, Bottazzo GF, Doniach D; Clinical significance of mitochondrial antibodies in relation to liver disease. Lancet 1981; ii: 804.