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Case Report

Liver Schistosomiasis and Primary Biliary Cirrhosis

A Clinico-Pathological Study

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Summary. The case of a patient suffering from liver schistosomiasis diagnosed by liver biopsies is presented. There were also lesions in the liver suggestive of non-suppurative destructive cholangitis and the serum-immunological studies strengthened the diagnosis of primary biliary cirrhosis. The co-existence of these two affections and their possible inter-relationship are discussed. The authors further discussed some clinical, biochemical, immunological and pathological aspects of these two conditions and evoked the eventuality of an auto-immune type of hepatic affection triggered by the presence of the schistosome eggs.

Key words: Liver — Schistosomiasis — Primary Biliary Cirrhosis — Antimitochondrial Antibodies.

The facility of international travel, the constant movement of people between and within continents and through different climatic regions create numerous medical problems and diagnostic difficulties.

The distribution of schistosomiasis, a parasitic disease of tropical and subtropical regions, is well defined. However, there are more and more cases being described outside these regions, which have been to some extent overlooked (Bianchi and Carnieri, 1970; Hamzei, 1971; Woodruff, 1970). In fact, there are four known types (S. mansoni, S. haematobium, S. japonicum, S. intercalatum) which affect man (Blanc and Nosny, 1967). The common histological lesions due to the four species of this parasite in various organs are well described (Edington and Gilles, 1969) and detailed descriptions of the different aspects of liver involvement in the various forms leading, in some instances, to fine fibrosis or the "clay-pipe-stem" cirrhosis described by Symmers in 1904 are well documented (Cheever and Andrade, 1967; Edington and Gilles, 1969; Manson-Bahr, 1966). In recent years, interest has shifted to the immunologic aspects of the disease (Smithers, 1972; Warren, 1972), and several authors have observed modifications of the immunoglobulins, or even the presence of anti-liver antibodies in certain instances of bilharzial liver fibrosis (Antunes *et al.*, 1971; Bassily *et al.*, 1973; Ghanem *et al.*, 1970).

The association of hepatic schistosomiasis and acute viral hepatitis has been described (Menhem *et al.*, 1973), but we were unable to find in the literature an association with the syndrome of primary biliary cirrhosis. Such an association and its immunological implications have prompted this report.

Case History

A 54 year-old Swiss housewife was admitted in January 1972 to investigate the origin of a severe osteoporosis with vertebral collapses and an elevated alkaline phosphatase. She had noticeable back pains for one year and has had a history of Raynaud's phenomenon since 1946. During the last 5 years she had travelled to Morocco, Madeira and the Canary Islands during her holidays.

On *physical examination*, there were no significant findings. Blood pressure was 120/80 mm Hg and the pulse rate was 80/min. Temperature was normal. The thoracic spine was painful on percussion but there were no neurological signs on compression.

Table 1

	1972				1973	
	Jan.	March	June	Oct.	April	August
Alc. phosphat. (15–54 U/l)	500	340	225	—	345	226
Tot. bilirub. (10 mg/l)	12.2	9.9	11.4	—	11.7	14.2
SGO/SGP (17 U/l)	33/33	11/25	33/32	—	26/33	18/14
Tot. prot. (63–78 g/l)	88.6	81.8	73.8	78	78.8	77.8
Albumin (46.1–61.3%)	47	46.7	49.5	46.7	47.3	43.8
$Alpha_1$ glob. (1.9–4.1%)	4.3	6.5	5.9	6.2	2.4	3.7
$Alpha_2$ (8.7–15.9%)	12.5	12.9	10.8	13.4	14.3	17.4
Beta (11.2–19.2%)	16.8	16.2	15.8	16.8	19.1	16.1
Gamma (11.2–20.4%)	19.4	17.7	18.0	16.9	16.9	19.0
IgM (126 ± 100 mg-%)	1040	520	380	568	310	410
IgA (195 ± 135 mg-%)	708	630	570	612	800	738
IgG (1230 ± 395 mg-%)	1420	1320	1170	1170	1370	1300
Anti-nucl. factor	1/10	1/1	1/1	neg.	neg.	—
Anti-smooth muscle	neg.	1/20	neg.	1/20	1/20	neg.
Anti-mitochondrial	1/80	1/160	1/20	1/160	—	1/320
Australia antigen	neg.	—	—	—	—	—
Australia antibody	neg.	—	—	—	—	—
Latex test	—	—	—	1/80	—	1/40
L.E. cells	—	—	—	—	—	neg.
Alpha-feto prot.	neg.	—	—	—	—	—
Immunofluor. test for bilharzia	1/20	1/20	—	1/10	neg.	—
Sedimentation rate	54/90	55/90	43/74	40/68	50/82	56/96

The *laboratory findings* revealed a raised E.S.R. at 54/90 mm (1st and 2nd hours); hemoglobin was 14.5 g-%; white blood cell count was 5950/mm³ (segmented 32%, non-segmented 5.5%, eosinophils 5.5%, basophils 0.5%, monocytes 11%, lymphocytes 45.6%) The platelet count was 198000/mm³. Urinalysis was normal and there were no bile pigments. The relevant biochemical and immunological findings are summarized in the table (column 1). This shows perturbed liver function tests, in particular an increased alkaline phosphatase and the presence of antimitochondrial antibodies. A needle liver biopsy revealed among other lesions the presence of calcified fragments of schistosome ova in a portal tract. A rectal biopsy was negative for ova and a bone biopsy was insufficient to permit interpretation. Biopsy of the bladder was not performed.

She did not recall having digestive troubles during recent years. She was never jaundiced and did not suffer from pruritus. Steatorrhoea was not found. Schistosome ova were not observed in the urine nor in the stools. An intravenous cholangiography showed a normal gallbladder and biliary tree. Roentgenograms of the skeleton revealed significant osteoporosis and collapse of the sixth, ninth and eleventh thoracic and first lumbar spines.

Because of the presence of schistosome ova in the liver and a positive immunofluorescence test for schistosomiasis, the patient received a full course of niridazole (Ambilhar®), 25 mg/kg/day during 10 days. A second liver biopsy performed 2 months later showed viable schistosome ova which necessitated a second course of niridazole. The immunofluorescence test for schistosomiasis became negative but there was no significant improvement in the results of laboratory tests over the next 20 months as can be seen in the table. This warranted a third liver biopsy, which will be described with the other biopsies below.

Pathology

Needle puncture of the liver, as well as biopsies of the rectal mucosa and iliac crest were performed in order to establish the diagnosis shortly after admission. A second rectal biopsy was performed 8 days later and a second liver biopsy two months afterwards. A third liver biopsy was performed 12 months after the second.

The *first liver biopsy* showed significant abnormalities. The portal tracts, in areas, were diffusely infiltrated by mononuclear cells (lymphocytes and plasmocytes) and few eosinophils. There was little or no extension into the surrounding lobule and the limiting plates were intact. In two areas, portal tracts presented partial destruction of the large bile ducts or abnormal bile ducts with partial destruction of the epithelium suggestive of chronic non suppurative destructive cholangitis (Fig. 1a, b). There was no bile duct proliferation. Certain portal tracts contained sheaths or nests of macrophages giving them a granulomatous appearance (Fig. 2a, b). On the edge of a partially hyalinized tract there were lamellated, somewhat stratified, calcified elements which were highly suggestive of calcified schistosome ova.

Within the lobules there were isolated foci of hepatic cell necrosis surrounded by chronic inflammatory cells and in some instances a moderate fibroblastic reaction. There was no modification of the liver cell plates and the Prussian blue stain did not show iron pigment. There was no cholestasis.

A *second liver biopsy* showed identical lesions, but in somewhat lesser degree. The portal tract infiltration was less pronounced and there was some degree of sclerosis. A few presented a granulomatous appearance with epitheloid cells and chronic non-specific inflammatory inflammation but there were no giant cells (Fig. 3a, b). The most important findings in the sections were the presence of calcified sections of schistosome ova and viable sections of eggs separated from the tissue (Fig. 4a, b).

The *third liver biopsy* 12 months later, showed occasional intralobular aggregates of chronic inflammatory cells and a persistance of portal tract infiltrates comparable to those observed in the first biopsy with some "bridging" (Fig. 5). There was a moderate increase in the bile duct within a few portal tracts.

The *rectal biopsies* performed shortly after admission at 8 days intervals were not revealing and the bone biopsy was too scanty in amount to permit valuable interpretation.

Discussion

Schistosomiasis, a chronic helminthic disease, is widely distributed in the Tropics and Orient and, besides malaria, has very high morbidity on the population in the areas where it is found.

The disease is caused by a trematode whose life cycle and mode of transmission in man are well known (Edington and Gilles, 1969; Manson-Bahr, 1966). The basic histologic lesion is a cell mediated immune granulomatous reaction to the

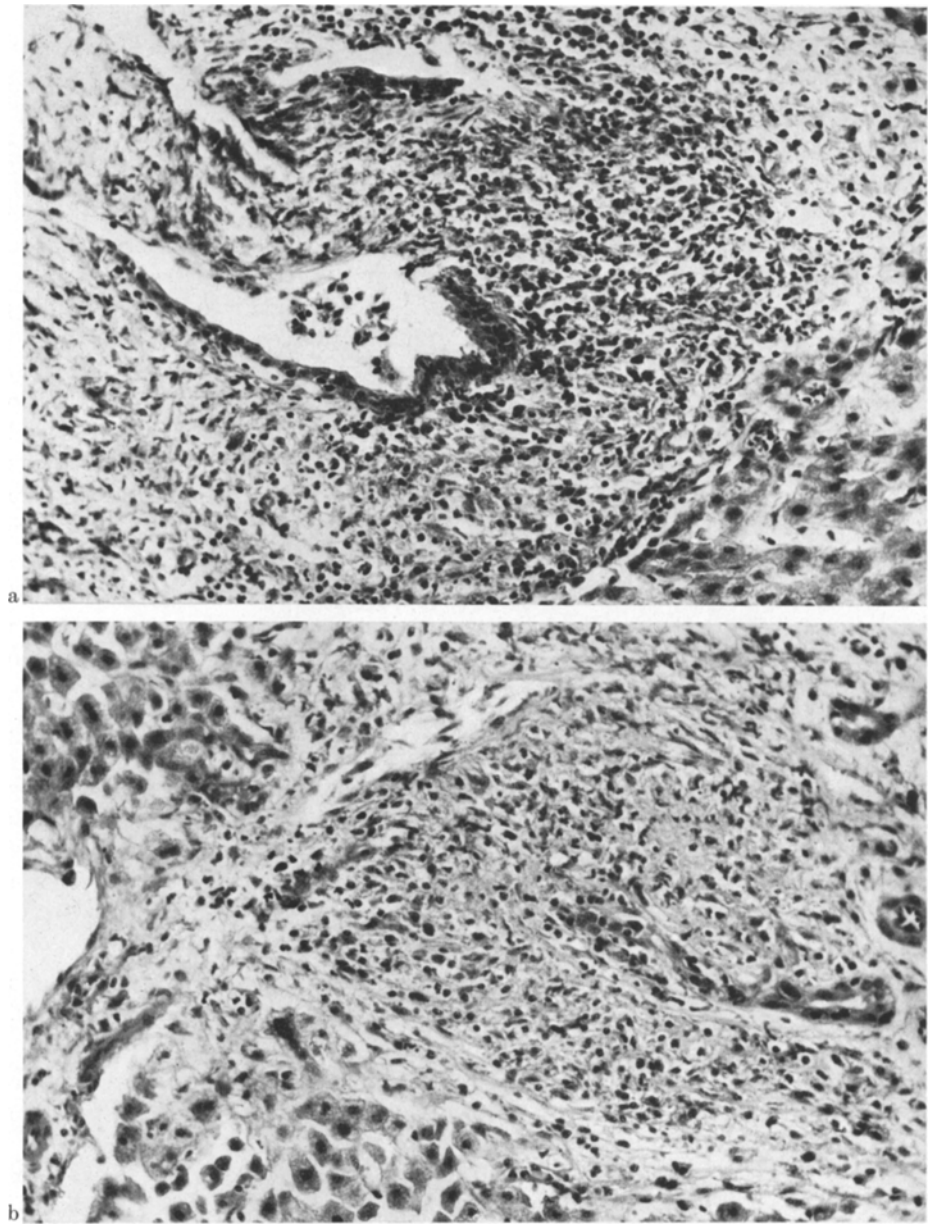

Fig. 1a and b. First liver biopsy. a Partial destruction of large interlobular bile duct with diffuse chronic inflammation of portal tract and conservation of limiting plate (H.E., ×120). b Destruction of bile duct surrounded by chronic inflammation (H.E., ×120)

schistosome ova (Smithers, 1972; Warren, 1968). Furthermore, Domingo *et al.* (1967) have shown that a similar reaction can also be introduced by soluble extracts from schistosome ova or inhibited by immunosuppressive drugs.

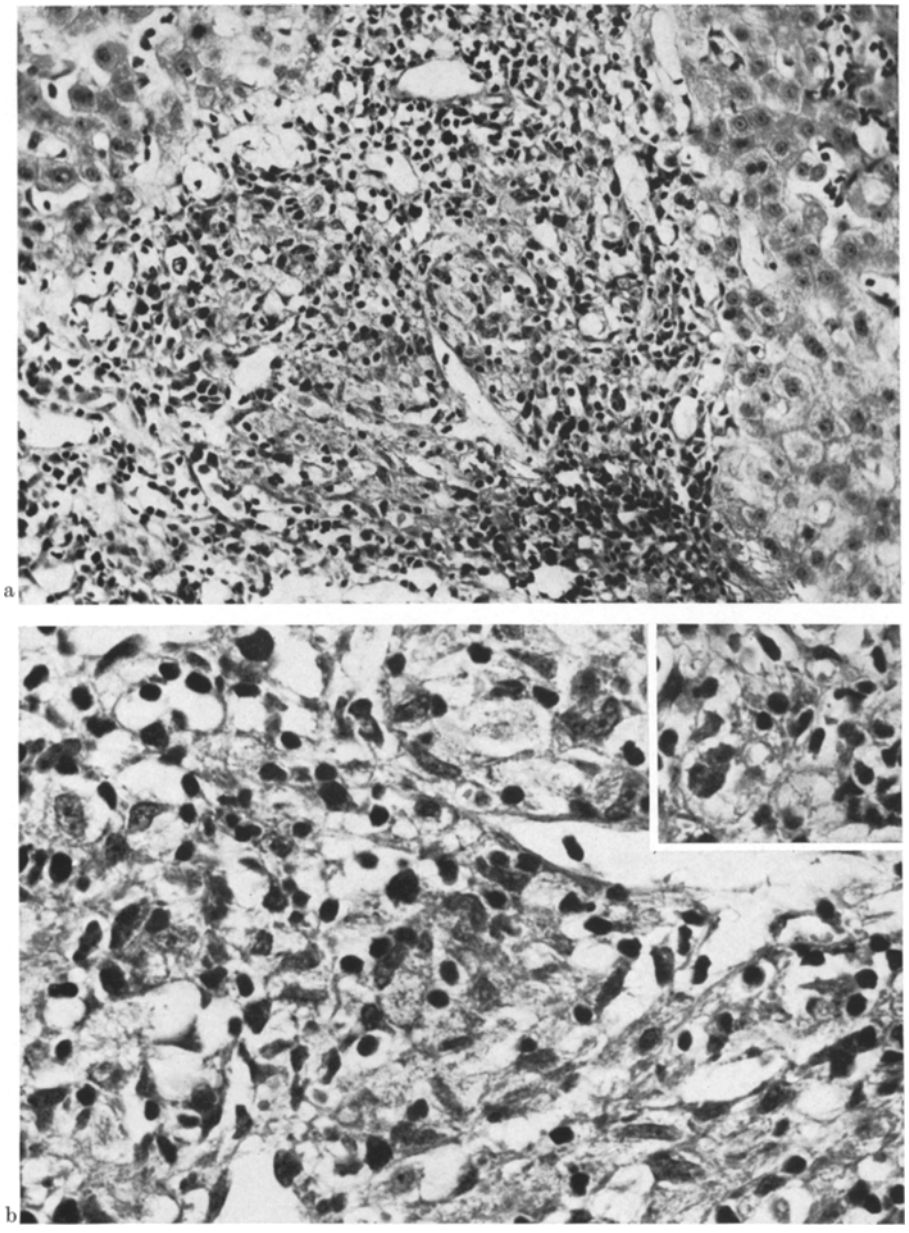

Fig. 2a and b. First liver biopsy. a Enlarged portal tract with aggregates of lymphoid cells numerous lipid-laden foam macrophages (H.E., ×120). b Lipid-laden macrophages in portal tract giving it a granulomatous appearance (H.E., ×240). Inset: Occasional giant cell

In the case under discussion, the patient presented hepatic lesions and serological reactions which confirmed the diagnosis of schistosomiasis, which she may have contracted during one of her voyages. It is very likely that this could

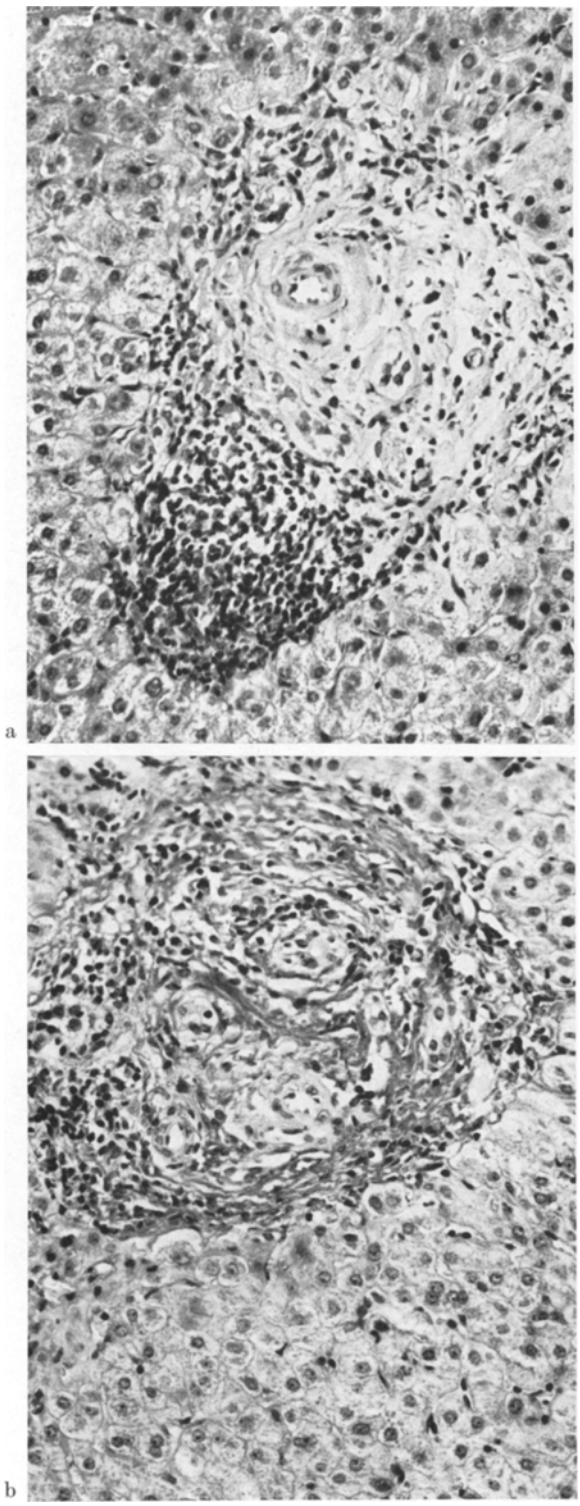

Fig. 3a and b. Second liver biopsy. Somewhat sclerosed portal tracts with aggregates of lymphoid cells (H.E., ×120)

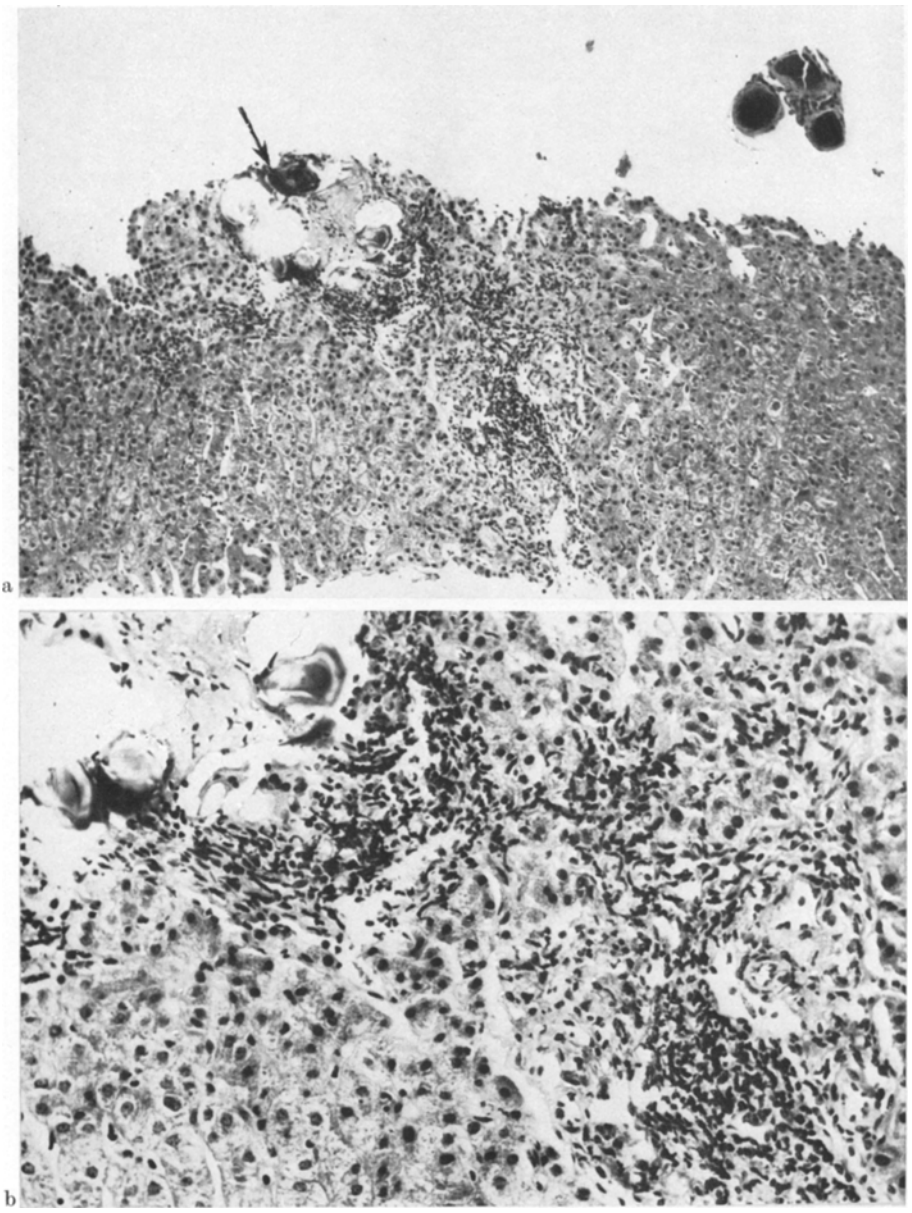

Fig. 4a and b. Second liver biopsy. a Calcified fragments of schistosome ova in upper left hand corner (↓). Removed from the fragment of liver tissue are viable sections of schistosome ova (H.E., ×60). b Detail of (a) showing calcified fragments of schistosome ova (H.E., ×120)

have been in Morocco, the only country, among those which she has been visiting in recent years, known to be infested with one of this parasite (S. haematobium) (Ansari, 1973).

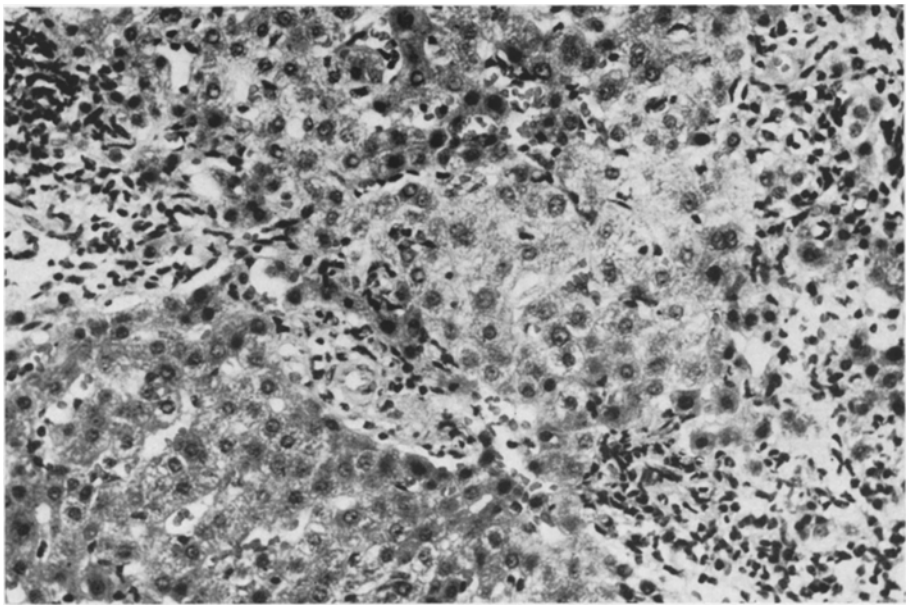

Fig. 5. Third liver biopsy. Continuing process one year later showing a histiocytic infiltration of the portal tracts with moderate non-specific inflammatory reaction and some degree of "bridging" (H.E., ×120)

S. haematobium is known to affect principally the urinary system, however, it is not uncommon to find eggs in other parts of the body including the intestine, lung and liver (Edington *et al.*, 1970; Gelfand, 1967; Payet and Camain, 1967).

In endemic regions, the disease presents very different aspects and can remain asymptomatic until diffuse fine fibrosis or "clay-pipe-stem" cirrhosis are installed with eventual portal hypertension (Garcia-Palmieri and Marcial Rojas, 1962). There is usually a significant modification in the serum proteins with a hypoalbuminaemia and a rise in serum globulins especially of the gamma fraction, so that the A/G ratio can be significantly reduced or even inverted (Garcia-Palmieri and Marcial Rojas, 1962; Ghanem *et al.*, 1970). Saif *et al.* (1964) have shown that the S.G.O.T. and S.G.P.T. are also raised in cases of liver involvement and that they ran parallel to the course of the disease. Barreto (1971) has pointed out the correlation between the liver involvement and alkaline phosphatase, as well as the correlation between this serum enzyme and the serum gammaglobulin fraction. However, he did not consider the raised alkaline phosphatase diagnostic of the disease, but rather as a means of evaluating prognosis.

Antunes *et al.* (1971) found elevated IgM and IgG in the acute stage, but normal values during the chronic phase, while Hillyer (1969) and Bassily *et al.* (1973) found high titers of these immunoglobulins even in the late stages of the disease. There is little or no modification of the IgA (Bassily *et al.*, 1972).

The patient under discussion, in spite of high serum proteins, does not show any significant modification of the A/G ratio. There are, however, constantly high values for IgM and IgA, but the IgM levels dropped considerably after

treatment for her bilharziasis. IgG remained always within normal limits. These findings are probably related to some chronic liver disease and not necessarily to her schistosomiasis.

The finding of a positive anti-mitochondrial antibody raises the possibility of the diagnosis of primary biliary cirrhosis (Doniach *et al.*, 1966; Gall and Mostofi, 1973; Paronetto, 1973; Popper and Schaffner, 1965; Sherlock, 1970). Furthermore, 6 of 22 proved cases of schistosomiasis treated for one of the four species of schistosome in our clinics were found to have liver involvement on biopsy. Of these, only the patient under discussion presented elevated titers of serum anti-mitochondrial antibodies. The presence of this serum antibody together with the liver biopsy appearance and the raised alkaline phosphatase, all argue in favour of primary biliary cirrhosis. In fact, outside those areas containing ova, the liver lesions are not those habitually observed in schistosomiasis, but rather those classically described in primary biliary cirrhosis (Baggenstoss *et al.*, 1972; Christoffersen *et al.*, 1972; Goudie *et al.*, 1966; Scheuer, 1968). Sherlock and Scheuer (1973) have shown that the diagnosis of primary biliary cirrhosis can be made early, even before the first clinical signs, on the grounds of the liver biopsy appearances and the presence of a positive serum-antimitochondrial antibody. Furthermore, Fox *et al.* (1973) have shown that primary biliary cirrhosis can be totally asymptomatic and that the diagnosis could be made only on biological and histological grounds. In the case under discussion, all the biological and histological criterias laid down by these authors are fulfilled. IgM is usually elevated in primary biliary cirrhosis (Feizi, 1968) while IgG and IgA remain normal (Thaler, 1973). Some authors (Bouchier *et al.*, 1964; Holborow *et al.*, 1963) have also indicated the presence of antinuclear factor and a positive latex test in primary biliary cirrhosis. In our case, the latex test was significantly elevated on two occasions, further strengthening this diagnosis.

Besides primary biliary cirrhosis, antimitochondrial antibody can be found in other chronic affection of the liver, principally active chronic hepatitis, cryptogenic cirrhosis and to a lesser extent in longstanding extrahepatic biliary obstruction, but these conditions can be excluded on histological, biological and immunological grounds (André *et al.*, 1973; Doniach and Walker, 1969; Kui Chun Lam *et al.*, 1972; Sherlock and Scheuer, 1973).

In this patient, the clinical history does not concur with that of primary biliary cirrhosis; however, the liver tests, the immunological findings and the histological appearances all point to this diagnosis, and therefore, it is quite possible that we are dealing with a case which could fall in the group of asymptomatic primary biliary cirrhosis described by Fox *et al.* (1973).

It is quite possible then that we are dealing with two different disease entities. On the one hand, a parasitic infection due to schistosomiasis contracted overseas, and on the other, a non suppurative destructive cholangitis under its asymptomatic form. One is however tempted to postulate that the patient contracted schistosomiasis and that the lesions produced by the eggs in the portal tracts have triggered the biological and immunological reactions suggestive of primary biliary cirrhosis. Tsutsumi (1971) has shown experimentally that massive infection of the liver with S. japonicum in rabbits provoked considerable damage to the vascular bed and the surrounding portal tract before cirrhosis was established. The changes are due partly to the local obstruction by the eggs and largely to the antigen-antibody complexes formed around the eggs. The host's reaction to the eggs thus determines the pathogenesis of the disease (Lichtenberg, 1970; Smithers, 1972; Warren, 1968), and the granuloma formation observed in the liver and lung was shown to be due to a type of delayed hypersensitivity (Domingo *et al.*, 1967; Warren, 1972). Von Lichtenberg (1969) also demonstrated humoral antibody in the precipitate, Hoeppli phenomenon, around the egg.

Deconinck *et al.* (1970) have described a case of schistosomiasis with biological and immunological reactions somewhat similar to those observed in our patient, and they concluded that the schistosomiasis had induced two types of reaction: a cellular immune reaction responsible for the formation of granulomas, and the synthesis of humoral antibodies. Evidently, there may be numerous factors taking part in these processes. The reaction of the host could play an important role and may vary from one individual to another and probably between those living in endemic regions and those coming into contact temporarily and later with the parasite. The parasitic strains may also play a role in the type of lesions produced, for it has been shown that strains from different regions provoke quite different anatomical lesions in patients as well as in experimental animals (Cheever and Andrade, 1967; Edington *et al.*, 1970). It is still not obvious why the same strain in a geographic region creates, in the liver, a fine hepatic fibrosis in certain individuals while in others a "clay-pipe-stem" cirrhosis. These factors suggest that there must be host specificity to the particular type of reaction depending evidently on the type and strain of schistosomiasis involved.

The presence of schistosome ova in two liver biopsies makes the diagnosis of bilharzia unquestionable in this patient. The liver lesions outside of these areas are consistent with those of primary biliary cirrhosis, the two disease entities thus occurring concomitantly. Since it is impossible to assert the date of onset of either of the conditions, it would be important in the future to determine autoantibodies, and in particular, antimitochondrial antibodies, not only in primary biliary cirrhosis and other chronic liver diseases, but also in cases of schistosomiasis of the liver.

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References

André, D., Salassola, D., Trepo, Ch., Sapetjian, M., Monier, J. C., Thivolet, J.: Signification des anticorps anti-mitochondries en pathologie hépatique et au cours de la syphilis. Path. et Biol. **21**, 697–706 (1973)

Ansari, N.: Epidemiology and control of schistosomiasis (Bilharziasis), p. 51. Basel/New York: S. Karger 1973

Antunes, L. J., Reis, A. P., Pellegrino, J., Tavares, C. A., Katz, N.: Immunoglobulins in human schistosomiasis mansoni. J. Parasit. **57**, 539–549 (1971)

Baggenstoss, A. H., Soloway, R. D., Summerskill, W. H. J., Elveback, C. R., Shoenfield, L. J.: Chronic active liver disease. The range of histologic lesions, their response to treatment, and evolution. Human Path. **3**, 183–198 (1972)

Barreto, V. S. T.: Alkaline phosphatase in schistosomiasis. Ann. intern. Med. **74**, 450–451 (1971)

Bassily, S., Higashi, G. I., Farid, Z., Williams, R. E.: Serum immunoglobulins in schistosomiasis mansoni. J. trop. Med. Hyg. **75**, 73–75 (1972)

Bassily, S., Mosiran, Y. Z., Said, M. I., Moussa, M., Iskander, F., Mooro, H.: Autoantibodies in schistosomal liver fibrosis. J. trop. Med. Hyg. **76**, 153–155 (1973)

Bianchi, L., Carnieri, I. de: "Imported schistosomiasis". Trans. roy. Soc. trop. Med. Hyg. **64**, 650–651 (1970)

Blanc, F., Nosny, Y.: Nosographie des schistosomes. Ann. Soc. belge Méd. trop. **47**, 17–34 (1967)

Bouchier, I. A. D., Rhodes, K., Sherlock, S.: Serological abnormalities in patient with liver disease. Brit. med. J. **I**, 592–594 (1964)

Cheever, A. W., Andrade, Z. A.: Pathological lesions associated with schistosoma mansoni infection in man. Trans. roy. Soc. trop. Med. Hyg. **61**, 626–639 (1967)

Christoffersen, P., Poulsen, H., Scheuer, P. J.: Abnormal bile duct epithelium in chronic aggressive hepatitis and primary biliary cirrhosis. Human Path. **3**, 227–235 (1972)
Deconinck, J., Wybran, J., Lustman, G. F.: Schistosomiase et manifestations immunologiques. Acta clin. belg. **25**, 241–252 (1970)
Domingo, E. O., Cowan, R. B. T., Warren, K. S.: The inhibition of granuloma formation around schistosoma mansoni eggs. I: Immunosuppressive drugs. Amer. J. trop. Med. Hyg. **16**, 284–292 (1967)
Doniach, D., Roitt, I. M., Walker, J. G., Sherlock, J.: Tissue antibodies in primary biliary cirrhosis, active chronic (lupoid) hepatitis, cryptogenic cirrhosis and other liver diseases and their clinical implications. Clin. exp. Immunol. **1**, 237–262 (1966)
Doniach, D., Walker, J. G.: A unified concept of autoimmune hepatitis. Lancet **1969 I**, 813–815
Edington, G. M., Gilles, H. M.: Pathology in the tropics, p. 129. London: Edward Arnold 1969
Edington, G. M., Lichtenberg, F. v., Nwabuebo, I., Taylor, J. R., Smith, J. H.: Pathologic effects of schistosomiasis in Ibadan, Western State of Nigeria. Amer. J. trop. Med. Hyg. **19**, 982–995 (1970)
Feizi, T.: Immunoglobulins in chronic liver disease. Gut **9**, 193–198 (1968)
Fox, R. A., Scheuer, P. J., Sherlock, S.: Asymptomatic primary biliary cirrhosis. Gut **14**, 444–447 (1973)
Gall, E. A., Mostofi, F. K.: The liver. International academy, p. 353. Baltimore: Williams & Wilkins 1973
Garcia-Palmieri, M. R., Marcial Rojas, R. A.: The protean manifestations of schistosomiasis mansoni. Ann. intern. Med. **57**, 763–775 (1962)
Gelfand, M.: Some remarks on the clinical and pathological aspects of schistosomiasis in Central Africa. Bilharziasis (F. K. Mostofi, ed.), p. 104. Berlin-Heidelberg-New York: Springer 1967
Ghanem, M. H., Guirgis, F., El-Sawy, M.: Assessment of liver functions in bilharzial hepatic fibrosis. Alexandria med. J. **16**, 117–136 (1970)
Goudie, R. B., MacSween, R. N. M., Goldberg, D. M.: Serological and histological diagnosis of primary biliary cirrhosis. J. clin. Path. **19**, 527–538 (1966)
Hamzei, R. B.: Bilharzia-Infektion zweier Deutscher nach Arbeitsaufenthalt in Afrika. Med. Klin. **66**, 171–173 (1971)
Hillyer, C. V.: Immunoprecipitins in schistosoma mansoni infections. Exp. Parasit. **25**, 376–381 (1969)
Holborow, E. J., Asherson, G. L., Johnson, G. D., Barnes, R. D. S., Carmichael, D. S.: Antinuclear factor and other antibodies in blood and liver diseases. Brit. med. J. **1963 I**, 656–658
Kui Chun Lam, M. B., Mistilis, S. P., Perrott, N.: Positive tissue antibody tests in patients with prolonged extrahepatic biliary obstruction. New Engl. J. Med. **286**, 1400–1401 (1972)
Lichtenberg, F. v.: The bilharzial pseudotubercle: a model of the immunopathology of granuloma formation. Immunologic aspects of parasitic infections. PAHO scient. Public. **150**, 107–127 (1967)
Lichtenberg, F. v.: Portal hypertension and schistosomiasis. Ann. N.Y. Acad. Sci. **170**, 100–114 (1970)
Manson-Bahr, P. H. Sir: Parasites of the circulatory system: schistosomiasis (bilharziasis), chap. 42. Manson's tropical diseases. A manual of the diseases of warm climates. London: Baillière, Tindall and Cassel 1966
Menhem, M. J., Bettez, P., Brazeau, M., Rousseau, B.: Infection à schistosoma mansoni et hépatite virale. Un. méd. Can. **102**, 392–394 (1973)
Paronetto, F.: Immunologic aspects of liver disease. Postgrad. Med. **53**, 156–161 (1973)
Payet, M., Camain, R.: Bilharziasis in French speaking West Africa. Bilharziasis (F. K. Mostofi, ed.), p. 133. Berlin-Heidelberg-New York: Springer 1967
Popper, H., Schaffner, F.: Progress in liver diseases, p. 522. New York/London: Grune & Stratton 1965
Saif, M. A., Abdallah, A., El Rooby, A., Shakier, M., Tawfik, J., Sabet, S.: Serum transaminases in bilharziasis and the immediate effect of antibilharzial treatment. Z. trop. med. Parasit. **15**, 199–207 (1964)

Sherlock, S.: Diseases of the liver and biliary system, p. 305, 4e ed. London: Blackwell 1970
Sherlock, S., Scheuer, P.: The presentation and diagnosis of 100 patients with P.B.C. New Engl. J. Med. **289**, 674–678 (1973)
Scheuer, P. J.: Liver biopsy interpretation. p. 22. London: Baillière, Tindall & Cassell 1968
Smithers, S. R.: Recent advances in the immunology of schistosomiasis. Brit. med. Bull. **28**, 49–54 (1972)
Symmers, W.: Note on a new form of liver cirrhosis due to the presence of the ova of bilharzia haematobia. J. Path. Bact. **4**, 237–239 (1904)
Thaler, H.: L'hépatite chronique. Medizinische Prisma **3**, 2–26 (1973)
Tsutsumi, H.: Pathology of liver cirrhosis in experimental schistosomiasis Japonica. Acta path. jap. **21**, 243–255 (1971)
Warren, K. S.: Pathophysiology and pathogenesis of hepatosplenic schistosomiasis mansoni. Bull. N.Y. Acad. Med. **44**, 280–294 (1968)
Warren, K. S.: The immunopathogenesis of schistosomiasis: a multidisciplinary approach. Trans. roy. Soc. trop. Med. Hyg. **66**, 417–434 (1972)
Woodruff, A. W.: Helminthic infections imported into Britain. Trans. roy. Soc. trop. Med. Hyg. **64**, 217–219 (1970)

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