

The association between ulcerative colitis and chronic liver disease at Tygerberg Hospital

J. G. PEROLD, D. J. J. BEZUIDENHOUT, T. D. ERASMUS, B. D. MIDDLECOTE

Summary

Twenty consecutive patients with ulcerative colitis were evaluated at the Gastro-intestinal Clinic, Tygerberg Hospital, with special reference to the biochemical tests and histological findings in the liver.

Abnormal liver function tests warrant a liver biopsy, since the underlying liver disease influences the subsequent prognosis and treatment.

S. Afr. med. J., 61, 186 (1982).

Twenty consecutive patients with ulcerative colitis were evaluated at the Gastro-intestinal Clinic, Tygerberg Hospital, with special reference to the biochemical tests and histological findings in the liver. The results and a short discussion are presented.

Patients, methods and results

The association between chronic inflammatory bowel disease and liver disease is well documented.¹⁻⁵ Twenty consecutive

	Normal values	Case 1	Case 2	Case 3	Case 4
Bilirubin ($\mu\text{mol/l}$)	2,5-17,0	9	14	7	17
Aspartate transaminase (U/l)	0-40	76	88	70	60
Alanine transaminase (U/l)	0-53	37	102	79	38
Lactic acid dehydrogenase (U/l)	100-225	409	184	188	476
Alkaline phosphatase (U/l)	30-85	312	271	1 104	65

Gastro-intestinal Clinic and Departments of Internal Medicine and Anatomical Pathology, Tygerberg Hospital and University of Stellenbosch, Parowvallei, CP

J. G. PEROLD, M.B. CH.B., M.MED.

D. J. J. BEZUIDENHOUT, M.D.

T. D. ERASMUS, M.B. CH.B., M.MED.

B. D. MIDDLECOTE, M.B. CH.B., M.MED.

Date received: 15 July 1981.

patients with ulcerative colitis (10 Whites, 9 Coloureds and 1 Indian) were included in the study. Liver function tests were done routinely, but only 4 of the patients were found to have biochemical abnormalities (Table I).

Bromsulphalein (BSP) retention tests were performed on the remaining 16 patients. In 10 of these the results were normal, but in 6 patients the BSP retention after 45 minutes was higher than the upper limit of normal of 5%. Thus a total of 10 of the 20 patients with ulcerative colitis had abnormal biochemical test results. These 10 patients were further investigated.

Serum protein electrophoresis. Patients 1, 3 and 4 had polyclonal gammopathy with raised IgG, IgA and IgM levels (Fig. 1).

Haematological investigation. Two of the patients were anaemic (Fig. 2) and 2 had raised erythrocyte sedimentation rates (Fig. 3).

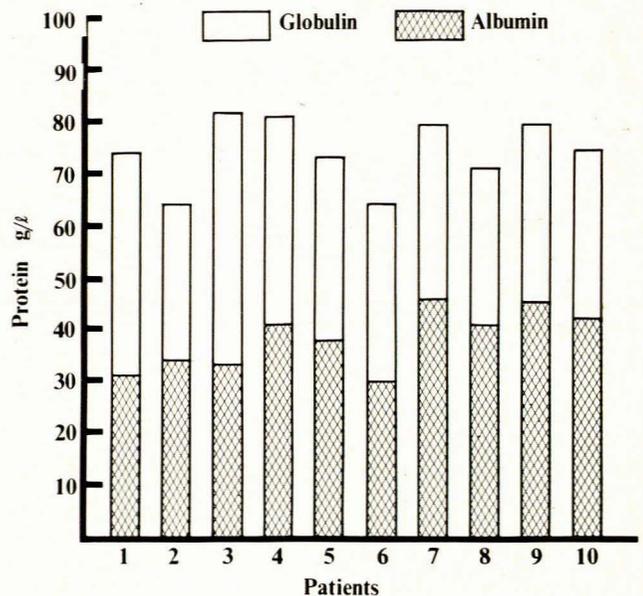


Fig. 1. Serum total protein values.

Immunological tests. Antinuclear factor (ANF) and anti-smooth muscle (ASM) antibodies were present in 1 patient (case 4), but none of the other antibodies tested for (antimitochondrial, anti-parietal cell, antithyroglobulin and antimicrosomal) were found.

Histological findings

Percutaneous liver biopsies using a Menghini needle were performed on 10 patients. Tissue was fixed in 10% neutral buffered formalin. All sections were routinely stained with haematoxylin and eosin, periodic acid-Schiff, Gordon and Sweet's reticulin stain, Perls' Prussian blue and Masson's trichrome. In 7 patients the morphological findings were

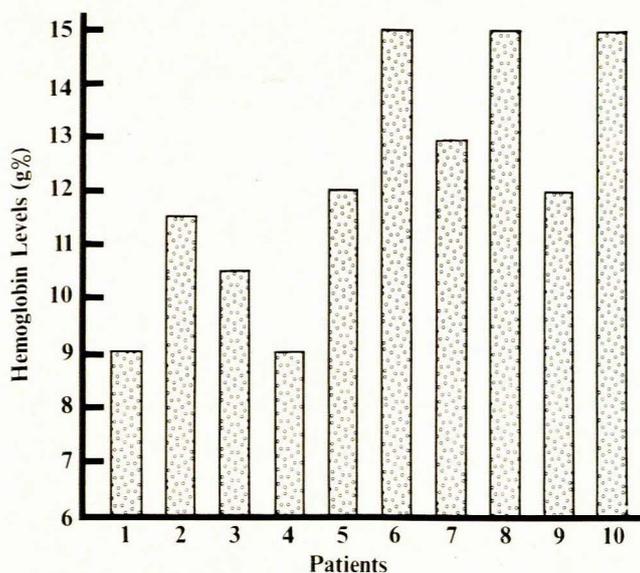


Fig. 2. Haemoglobin concentration.

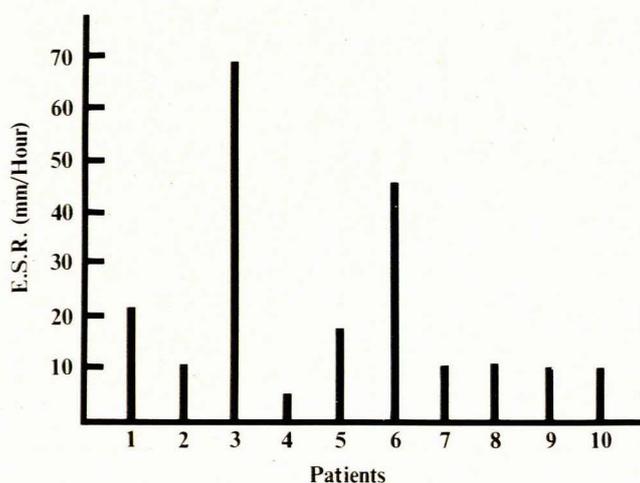


Fig. 3. Erythrocyte sedimentation rate.

essentially similar. Varying degrees of hepatocellular swelling, and in 2 cases mild fatty change, were present. Bile pigment was visible in varying amounts, predominantly in the centrilobular areas. No other morphological changes of note were detected. There seemed to be no good correlation between the severity of the bowel disease, the results of the biochemical function tests and the histological findings.

Three cases were noteworthy because of the histological findings. The case histories of the patients and morphological observations are presented below.

Case reports

Case 1

A 20-year-old Coloured man presented in 1974 with a history of loose stools with blood and mucus. On examination he had koilonychia and was clearly anaemic. Systemic examination was negative, but on sigmoidoscopy he was found to have grade 3 ulcerative colitis. Haematological examination confirmed an iron deficiency. Liver function tests showed a raised aspartate transaminase level (Table I). Needle biopsy of the liver showed moderately swollen hepatocytes and a portal inflammatory infiltrate consisting predominantly of lymphocytes. The

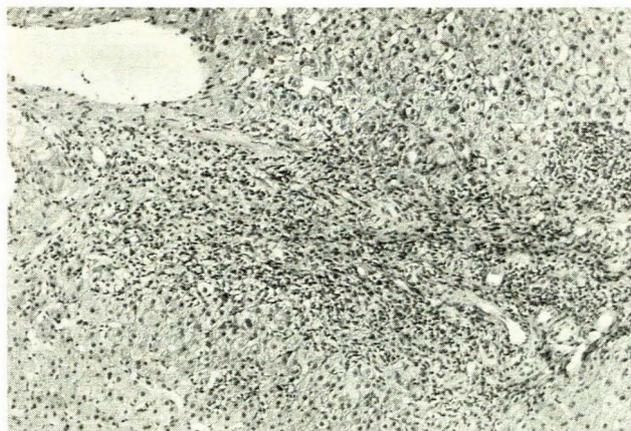


Fig. 4 (case 1). The inflammatory infiltrate and fibrosis bridging the portal tracts (H and E x 100).

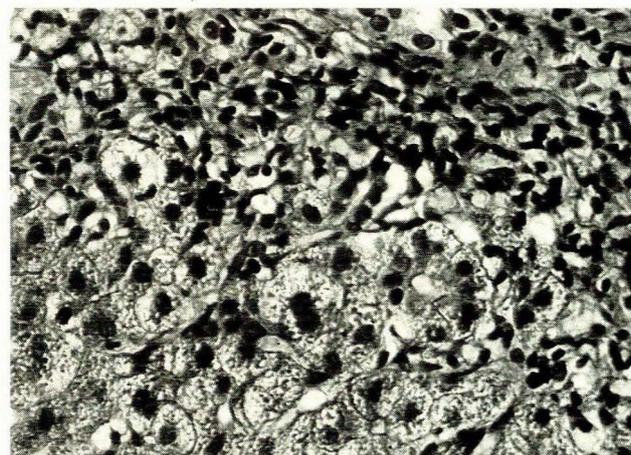


Fig. 5 (case 1). Irregularity of the limiting plate with fibrosis extending into the parenchyma and piecemeal necrosis (H and E x 100).

infiltrate extended from the portal triad into the surrounding parenchyma and piecemeal necrosis was noted. The portal triads were connected by fibrotic bands and mild bile duct proliferation was visible (Figs 4 and 5). Orcein-Shikata staining for hepatitis B (surface) antigen (HBsAg) was negative. The histological picture therefore suggested chronic active hepatitis and early macronodular cirrhosis. The patient was treated with sulphasalazine (Salazopyrin) and prednisone with rapid improvement, and remission is maintained on sulphasalazine 500 mg/d.

Case 2

This elderly White man had previously presented with ulcerative colitis in the mid-1960s. Control of the disease had posed no problem, but in 1976 a firm, non-tender hepatomegaly without signs of portal hypertension was evident. Liver function tests showed raised transaminase levels (Table I) and on needle biopsy the liver was found to be histologically similar to that described in case 1, but the degree of fibrosis was less. In addition, a small epithelioid granuloma, not associated with a portal triad and without specific morphologically identifiable features, was noted (Fig. 6). Appropriate special stains demonstrated no aetiological agent; the significance of this finding is uncertain. Orcein-Shikata staining for HBsAg was negative. The diagnosis of chronic active hepatitis with accompanying fibrosis was made.

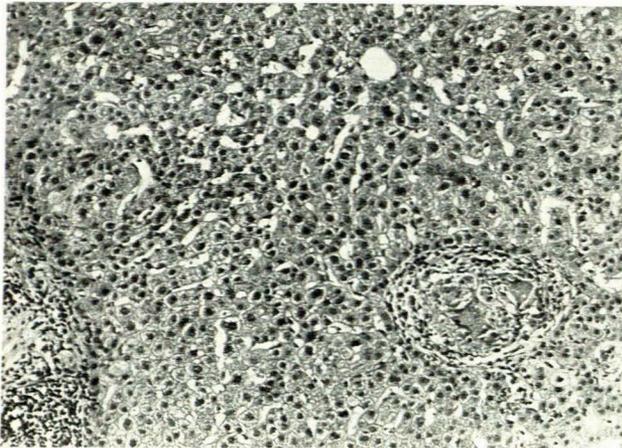


Fig. 6 (case 2). Inflammatory infiltrate and the epithelioid granuloma, unassociated with central vein or portal tracts. (H and E x 100).

Case 3

A 48-year-old White woman presented in 1975 with episodic diarrhoea accompanied by the passage of blood and mucus. Since 1977 she has had several episodes of fever, rigors, upper abdominal pain and jaundice. Liver function tests showed that the jaundice was obstructive in nature (Table I). Endoscopic retrograde cholangiopancreatography was negative and no biliary stones were demonstrated.

Sigmoidoscopy, performed during a remission of the symptoms, showed slight mucosal changes suggestive of ulcerative colitis and the diagnosis was confirmed histologically.

On histological examination of the needle biopsy specimen of the liver, the hepatocytes were swollen and a mild portal inflammatory infiltrate was noted which consisted predominantly of lymphocytes and a few neutrophils. No bile duct proliferation was present and only a slight increase in periportal fibrous tissue was noted. Bile pigment was visible in the hepatocytes, located predominantly in the centrilobular area, and a single area of possible piecemeal necrosis was noted. The possibility of a diagnosis of pericholangitis was considered, but the evidence was considered to be insufficient and the histological changes were thought to be nonspecific. The patient has been taking sulphasalazine since December 1978 and has had only two mild attacks of jaundice since.

Discussion

Ulcerative colitis is a chronic inflammatory disease of the colon, of unknown cause. It has long been known to have other systemic manifestations, including involvement of the skin, the eyes, the joints, the liver and the pericardium.⁶

TABLE II. INCIDENCE OF ASSOCIATED LIVER DISEASE IN CASES OF CHRONIC BOWEL DISEASE

	Reported incidence (approximate)
Liver disease	
Fatty change	Over 50%
Pericholangitis	30-50%
Primary sclerosing cholangitis	Less than 1%
Chronic active hepatitis	1-2%
Cirrhosis	2-5%
Bile duct carcinoma	Risk of tumour increased 10-fold
Pylephlebitis and pyogenic inflammation	Rare

The association of ulcerative colitis and liver disease was first described in 1874.⁷ In a series of 720 patients with ulcerative colitis and 517 with Crohn's disease¹ the incidence of biochemical liver function abnormalities was 8.2%.

Histologically, a wide variety of abnormalities is found, as illustrated in Table II.

Fatty change in the liver

The incidence of hepatic fatty change varies considerably in various series — between 15% and 80%. The fact that many of these studies have been done on autopsy series may account for the higher figures. Fatty change is initially periportal in distribution and its development may be a nonspecific manifestation of the accompanying toxæmia, malnutrition and anaemia.⁸

In our group, fatty change was present in only 2 of the 10 patients, and to a very mild degree (Fig. 7). These patients had no other significant histopathological changes apart from bile stasis located predominantly in the centrilobular areas.

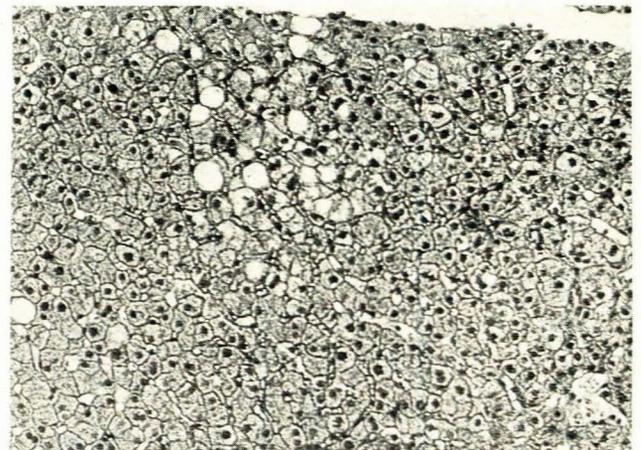


Fig. 7. The most severe degree of fatty change observed in this series (H and E x 100).

Pericholangitis

This term is now the generally accepted one, although the changes are not restricted to the biliary tree and in addition are difficult to delineate with certainty on a histological basis. The lesion has been referred to by several authors under different labels, i.e. interlobular hepatitis, portal triaditis, intrahepatic cholangitic hepatitis and toxic hepatitis.⁸

A mild inflammatory infiltrate in the portal tract is a relatively common occurrence and must be interpreted with caution. McSween⁸ refers to the work of Mistilis⁹ and Eade¹⁰ and suggests subdivision into acute, subacute and chronic lesions, even when the borders are ill-defined. Varying degrees of involvement may be seen in the adjacent portal tracts.

The mildest form of acute lesion shows an inflammatory infiltrate which may be predominantly periductal or around the portal vein. The infiltrate consists largely of lymphocytes with a few admixed plasma cells, macrophages and neutrophils.

As the lesion increases in severity, the infiltrate becomes more prominent and diffuse, but retains the tendency to focal condensation. Oedema is now present in the portal tract and degenerative epithelial change with cytoplasmic vacuolation may be noted in the bile duct. Polymorphonuclear neutrophils become more prominent.

In the chronic phase, the inflammatory infiltrate tends to spill over into the surrounding parenchyma; with subsequent irregularity of the limiting plate. Parenchymal changes are of a nonspecific nature and small areas of piecemeal necrosis may be

seen. The polymorphonuclear neutrophil infiltrate may become marked. Periductular fibrosis is now prominent and is loose in nature. This fibrosis may expand the portal tract, leading ultimately to portal-portal linkage with 'bridging portal hepatofibrosis'.¹¹ Progression to a biliary pattern of cirrhosis probably occurs, albeit only in a small proportion of cases.¹²

The changes in chronic active hepatitis may be difficult to separate from those in pericholangitis and both these conditions may be present concomitantly, as noted by Mistilis.⁹ Piecemeal necrosis may also be present in pericholangitis to a very mild degree; if it is a significant feature, a diagnosis of chronic active hepatitis should rather be made. The tendency of the inflammatory infiltrate to localize around the bile duct and portal veins and concomitant periductular fibrosis may simulate pericholangitis.

It is of interest that only 1 of our cases (case 3) partially fulfilled these criteria. This patient may have been in the so-called subacute stage.

Primary sclerosing cholangitis

This was first reviewed by Smith and Loe¹³ in 1965. It is a generalized disorder of the biliary tree involving both intrahepatic and extrahepatic ducts and even the gallbladder.¹⁴ The sclerotic process causes irregular narrowing of both the extra- and intrahepatic biliary tree. Histologically, transmural fibrosis and chronic inflammation of the major ducts is present. Pericholangitis and sclerosing cholangitis may represent the same condition affecting different parts of the biliary tree and can occur together.¹⁵

Chronic active hepatitis and miscellaneous

Chronic active hepatitis occurs occasionally (in 2 out of 20

patients in this series), while cirrhosis, biliary tract carcinoma and gallstones are infrequently associated with chronic inflammatory bowel disease. Epithelioid granulomas occur occasionally and were found in 1 of our patients.

Conclusion

Chronic bowel disease may be complicated by liver disease, and it is therefore important to perform liver function tests routinely on all patients with chronic bowel disease. However, it seems unnecessary to estimate BSP retention; estimation of serum alkaline phosphatase and transaminase levels suffices to distinguish patients that need further investigation. Liver biopsy should be performed on these patients, since the underlying liver condition influences the prognosis and treatment. Care should be exercised in the diagnosis of pericholangitis, as this may easily be confused with other conditions.

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Nuus en Kommentaar/News and Comment

Neurosyphilis today

It might be expected that with the resurgence of the sexually transmitted diseases neurosyphilis would become commoner. At the beginning of this century it accounted for up to 15% of admissions to psychiatric or neurological wards, but with the advent of effective treatment figures fell steadily. A 5-year survey of cases in Copenhagen (*Ugeskr. Laeger*, 1981, **143**, 2218) showed that any recent increase in cases was negligible. The 23 patients admitted to hospital over a 5-year period represent an incidence of only 0,30/100 000 population.

However, the study confirms that the diagnosis is difficult nowadays. The man with tabetic gait, absent knee jerks and Argyll-Robertson pupils is no longer seen, nor is the individual with characteristic delusions of grandeur. The presenting symptoms in the present series were quite varied, but the usual diagnosis was one of stroke (5 cases of hemiparesis), progressive dementia or acute psychosis (6 cases), or neuritis (4 patients complaining of pain in the arms and legs). Serological tests for syphilis are worth while in any neurological or psychiatric case in which there is even a remote diagnostic possibility, particularly in the younger patient with a stroke or the patient with unexplained dementia.

Hepatitis B virus and liver cancer

A co-operative study involving Johannesburg, Athens and New York has demonstrated the presence of DNA from hepatitis B virus (HBV) integrated into genomes of liver cells from patients with hepatocellular carcinoma (*New Engl. J. Med.*, 1981, **305**, 1067).

The sophistication of techniques now permits assessment of DNA sequences and integration patterns in percutaneous liver biopsy specimens. In the present study HBV-DNA analysis was performed on hepatocellular carcinomas from 20 rural mine workers from Mozambique as well as on 18 patients from the USA and Greece with various forms of liver disease.

In the specimens from patients with hepatocellular carcinoma integrated HBV-DNA was invariably found, but this was not the case in most HBV carriers with or without evidence of chronic liver disease. It may be that the integration state of HBV-DNA in biopsy specimens can help to identify those at increased risk of developing carcinoma. Diffuse integration into the genome may precede a stage in persistent HBV infection during which a specific subpopulation of liver cells divides into a clonal focus containing the integrated HBV; some other factor may then be involved in development of carcinoma at such a focus.