Membranous glomerulonephritis and chronic hepatitis

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Introduction

THE ASSOCIATION between chronic hepatitis and glomerulonephritis (GN) has recently been described[1-4]. We report two Malay patients with chronic hepatitis and membranous glomerulonephritis.

Case 1

M.F. a 47 year old Malay man was admitted to University Hospital after 7 months of intermittent swelling of the body. He had absolutely no other symptoms and no other previous illness. He had been a newscaster for 20 years in the Middle East and returned to Malaysia 4 years before his illness.

On admission, he had marked oedema of the legs up to the groins and gross ascites. There was no facial oedema, jaundice or spider naevus. He was afebrile, pulse was 92/minute and BP was 140/110. Soft small lymph nodes were palpable in the neck and both axillae.

The blood count was normal. ESR was 110 mm in the first hour, prothrombin time was 100%. Urine microscopy showed a few granular, hyaline and fat casts. 24 hour urine contained 15.3 grams protein. Serum albumin was 1.2 gram/100 ml, globulin 3.2 gram/100 ml. SGPT was 10 IU/100 ml, SGOT 10 IU/100 ml, alkaline phosphatase 87 IU/100 ml, total bilirubin was 0.3 mg/100 ml, cholesterol 860 mg/100 ml, urea 22 mg/100 ml, serum creatinine 0.8 mg/100 ml. Electrolytes were normal, LE cells were negative on 3 occasions. Serum hepatitis B surface antigen and antibody were positive. Rectal biopsy was negative for schistosoma and amyloid. Stools contained no ova. Intravenous urogram showed that the left and right kidneys were 14.5 cm and 14.0 cm respectively. There was notching of the left ureter and left renal vein thrombosis was confirmed by venography. Renal biopsy showed diffuse thickening of glomerular capillary walls, without increase in cellularity. Spike-like epimembranous projections of the basement membrane were present in sections stained with periodic acid silver methenamine and there were epimembranous deposits in sections stained with Masson's trichrome stain. Electron microscopy showed widespread epithelial foot-process fusion and many epimembranous electron dense deposits beneath the epithelial cell cytoplasm with extension of basement membrane material between the deposits (Fig. 1). Immunofluorescence showed IgG, IgM, IgA, IgD and IgE in a granular pattern along the glomerular basement membrane, and in the mesangium. In addition there were granular deposits of hepatitis B surface antigen (HBs Ag). (Fig. 2).

After the ascites subsided, a firm smooth liver could be felt 4 cm below the right costal margin and the spleen was palpable (1 cm) below the left costal margin. Needle biopsy of the liver revealed a macronodular cirrhosis with chronic active hepatitis. Some of the hepatocytes showed "ground glass cytoplasm" and these cells were positive to Shikata's orcein stain. Immunofluorescence studies confirmed the presence of HBs Ag in the cytoplasm of hepatocytes (Fig. 3).

Case 2

K.S. was a 24 year old Malay woman who was referred with a diagnosis of lupus nephropathy.

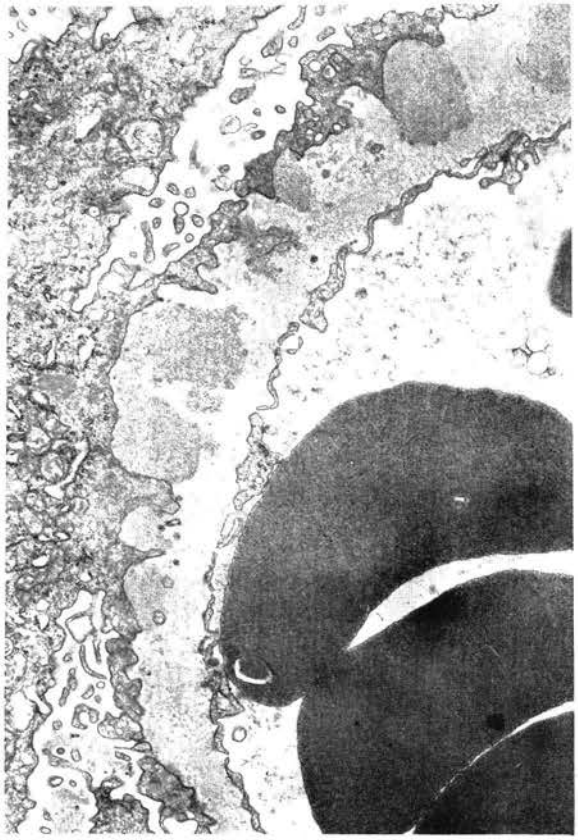

Fig. 1. Case 1. Electron micrograph of glomerular capillary wall showing thickening of the basement membrane and epimembranous electron dense deposits. × 10,000.

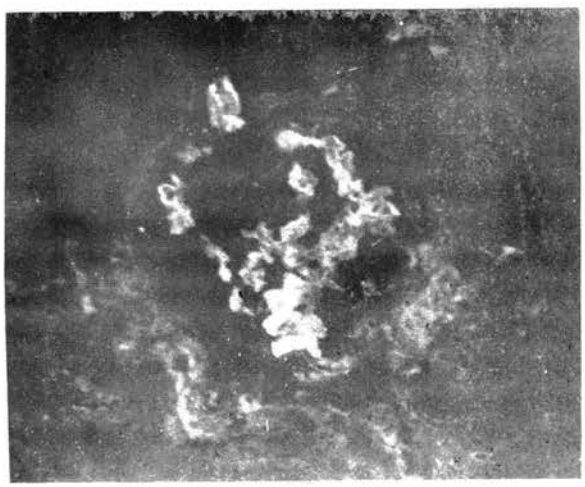

Fig. 2. Case 1. Indirect immunofluorescent staining for HBs Ag shows granular to lumpy deposits along the glomerular capillary wall. × 300.

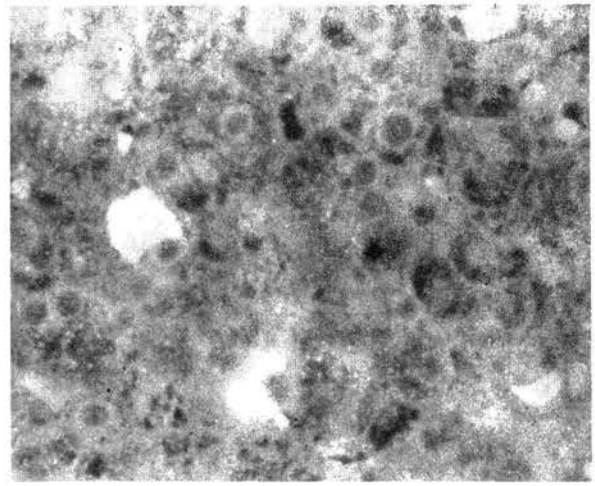

Fig. 3. Immunofluorescence of liver showing hepatocytes with HBs Ag in cytoplasm. (× 100).

The illness began with a short episode of fever and painful swelling of both elbows and the left knee, with an erythematous rash on the skin. This was followed, 10 weeks before admission, by progressive swelling of the legs and abdomen. She also had non-productive cough, increasing alopecia, loss of axillary and pubic hair and amenorrhoea for 4 months.

On admission the temperature was 37.5°C, pulse 86/minute and BP 140/85. She looked ill and was edematous and pale. There was no rash or jaundice. There was alopecia, the axillary and pubic hair was absent and the breasts were small. Heart and lungs were normal. The abdomen was distended with ascites and the liver had a span of 19 cm. It was firm but not tender. The spleen was just felt. Rectal examination was negative. She had 1-3 cm soft axillary and cervical lymph nodes. Central nervous system and the joints were normal.

Haemoglobin was 8.6 gm/100 ml, haematocrit 27%, total white 7,500/mm^3 with normal differential count. Platelet count was 298×10^3 per mm^3, reticulocyte count 1.9%. ESR was 25 mm in the first hour. LE cells was negative repeatedly. Serum C_3 was 20 mg/100 ml and C_4 was 10 mg/100 ml. Prothrombin time was 100%. There was no abnormal haemoglobin on electrophoresis. Blood film for malarial parasite was negative three times. Coombs test was negative. Urine contained 3 red blood cells and 20 white cells with an occasional granular and hyaline cast in each high power field. 24 hour urine protein was 4.4 gm. Serum protein was 6.0 gm/100 ml and albumin 1.5 gm/

100 ml. SGOT was 66 IU/100 ml, SGPT 2 IU/100 ml and alkaline phosphatase was 280 IU/100 ml. Bromsulphthalein test showed a retention of 14% in 45 minutes. Serum cholesterol was 220 mg/100 ml, urea 32 mg/100 ml, creatinine 0.7 – 0.9 mg/100 ml, fasting glucose 100 mg/100 ml, uric acid 9.5 mg/100 ml and electrolytes were normal. Plasma estrogen, protein bound iodine and cortisol levels were normal. Widal and Weil-Felix and VDRL were negative. Serum for HBs Ag and antibody were negative by counter immunoelectrophoresis. Chest and skull x-ray, blood and urine cultures were normal.

Needle biopsy of liver revealed chronic active hepatitis with progression to cirrhosis. The liver cell plates were hyperplastic and showed acinar formation. Some of the hepatocytes showed giant cell transformation. Orcein positive hepatocytes were not found in sections stained with Shikata's stain.

As in patient 1, the renal biopsy showed features of epimembranous nephropathy on light microscopy and this was confirmed by electron microscopy. In addition some of the endothelial cells contained virus-like microtubular structures (Fig. 4). Immunofluorescent studies were not done.

Comments

Alpert et al showed that the circulation of viral hepatitis antigen antibody complexes may give rise to fever, rash, joint pains and variable proteinuria as in serum sickness[5]. In some patients, this phase passes unnoticed and they present with the characteristic features of viral hepatitis. Others only present with cirrhosis and its complications[6]. Our first patient had no clinical sign or symptom of the liver disease and only presented with nephrotic syndrome. The other patient developed serum sickness like illness and membranous glomerulonephritis, probably from Hepatitis B infection.

It is now well accepted that membranous GN and the various forms of proliferative GN are the result of inflammatory changes associated with the deposition of immune complexes in the kidney. Since HBs Ag and antibody circulate as immune complexes it is not surprising that this can result in the development of membranous GN, as in our two patients. Indeed Brzosko et al found that only membranous GN and proliferative GN stained positive for HBs Ag whereas minimal change GN which is not associated with immune deposits, did not[7].

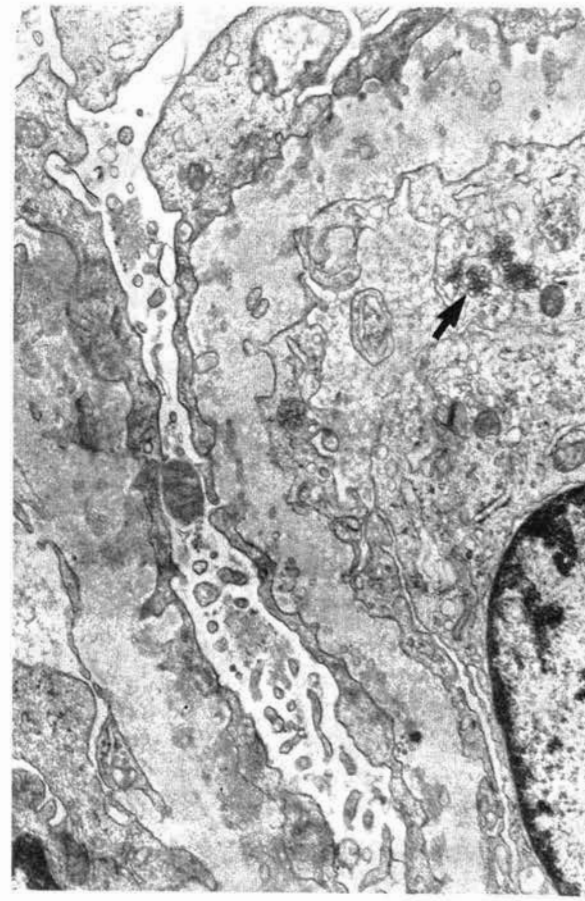

Fig. 4. Case 2. Electron micrograph of glomerular capillary wall showing irregular thickening of basement membrane and electron dense deposits. Virus-like microtubular structures are present in an endothelial cell (arrow). × 11,200.

It is now realised that the prevalence of positive hepatitis B surface antigen and antibody serum is high in the tropics[8] and orient[9,10] and if this reflects the incidence of chronic hepatitis viral infection, one would expect that HB or non-HB viral infection would be a more common cause of GN in our community than has been hitherto recognised.

Summary

Two Malay patients presented with ascites and proteinuria and were found to have membranous glomerulonephritis and chronic active hepatitis. In countries where the prevalence of viral B hepatitis is high, this may be an important cause of glomerulonephritis.

Acknowledgements

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References

1. Combes B, Statsny P, Shorey J, Eigenbrodt EH, Barrera A, Hull AR and Carter NW (1971): Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. *Lancet* **2:** 234.
2. Myers BD, Griffel B, Navek D, Jankielowitz T, Klajman A (1973): Membranoproliferative glomerulonephritis associated with persistent viral hepatitis. *Am. J. Clinical Pathology* **60:** 222.
3. Kneiser MR, Jenis EH, Lowenthal DT, Bancroft WH, Burns W, Shalhoub R (1974): Pathogenesis of Renal Disease associated with Viral Hepatitis. *Arch. Path.* **97:** 193.
4. Kohler PF, Cronin RE, Hammond WS, Olin D and Carr RI (1974): Chronic membranous glomerulonephritis caused by Hepatitis B antigen-antibody immune complexes. *Ann. Int. Med.* **81:** 448.
5. Alpert, E, Isselbacher KJ and Schur PH (1971): The pathogenesis of arthritis associated with Viral Hepatitis. *New Eng. J. Med.* **285:** 185.
6. Sheila Sherlock: The Chronic Hepatitides. Advanced Medicine – Suppl. 11 (1975). Ed. Lant AF. Pitman Medicine, London, pp 72.
7. Brzosko WJ, Krawczynski K, Nazarewicz T, Morzycka M, Nowoslawaski A (1974): Glomerylonephritis associated with Hepatitis B Surface Antigen immune complexes in children. *Lancet* **2:** 477.
8. Francis TI (1975): Epidemiology of Viral Hepatitis B in the Tropics. *Bull. N.Y. Acad. Med.* **51:** 501.
9. Letter: Chiewsilp P, Vinyan S, Bhamarapravati N (1974): Hepatitis antigen-antibody in Thai Blood Donors. *Trans. Royal Society Trop. Med. and Hygiene.* **68:** 339.
10. Lopez CG, Govindasamy S, Duraisamy G, Ee TI, Heng SH and Simons MJ (1976): Prevalence of hepatitis B infection as determined by third generation tests in the Malaysian population. 11th Malaysia-Singapore Congress of Medicine 1976, pp 59.