Postgraduate Medical Journal (1989), **65**, 14 - 15

Missed Diagnosis

Nephrotic syndrome and hepatitis in early syphilis

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Summary: A 54 year old man presented with features of acute hepatitis and the nephrotic syndrome. A diagnosis of active syphilis was only made by chance after extensive investigation. Syphilis should be considered in the differential diagnosis of both acute hepatitis and the nephrotic syndrome occurring separately as well as together.

Introduction

The nephrotic syndrome and hepatitis are rare features of early acquired syphilis and we are only aware of two previous reports of them occurring together in the same patient.[1,2] The following case presented a diagnostic problem and is reported as a reminder. If early syphilis increases, as has been reported recently in certain areas of the United States of America and in this department, such cases may become more frequent.

Case report

A 54 year old male Caucasian was admitted with a 6-week history of vomiting 30 minutes after meals and vague upper abdominal discomfort. Four weeks before admission, sallowness of his complexion had been noted, his stools had become pale and his urine dark. On referral to hospital, jaundice and a maculopapular rash were recorded, viral hepatitis was suspected, but urgent admission was precipitated by the rapid onset of ankle swelling and effort dyspnoea.

His previous health had been good, and he had no risk factors for hepatitis B. He was a diet-controlled diabetic who had remained well for over 10 years. He lived alone after separation from his wife 4 years before, and denied any sexual contact during that time.

Examination on admission revealed an icteric ill man with generalized lymphadenopathy and marked pitting oedema up to the knees. His rash had nearly resolved. No other abnormal signs were elicited, and urinalysis showed marked proteinuria and glycosuria.

The liver function tests were abnormal (normal values in brackets): alkaline phosphatase 100 KAU/l (2–11), bilirubin 187 μmol/l (<19), alanine transaminase (ALT) 48 U/l (<20). Hepatitis A IgM, hepatitis B surface antigen and heterophil antibody detection were all negative. Serum albumin was 26 g/l and urine protein excretion 10 g/24 hours. An abdominal ultrasound showed gall-stones in an undilated common bile duct and normal intrahepatic bile ducts. The kidneys were diffusely enlarged, but no other abnormality was detected. Over the next fortnight, he remained unwell with an intermittent, low-grade pyrexia. Timed blood cultures showed no pathogens. He became hyperglycaemic and required subcutaneous insulin. An endoscopic retrograde choledochopancreatogram (ERCP) demonstrated a normal biliary tree and pancreatic ducts though the gall-bladder did not fill with contrast. A renal biopsy showed normal glomeruli with haematoxylin and eosin staining under light microscopic examination. No spikes were seen in the silver methenamine stain.

Immunofluorescence showed diffuse IgG and C3 deposition in a granular pattern, mainly in the glomerular basement membrane. Electron microscopy demonstrated foot process fusion and widespread discrete subepithelial electron dense deposits. Computerized tomography did not demonstrate any tumour masses or collections of pus.

He was managed with diuretics and daily weighing until the beginning of the third week in hospital. His renal function was stable but the hepatic biochemical abnormalities persisted. Serum albumin was 16 g/l. He remained febrile and the cause remained unclear but

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Accepted: 25 August 1988

biliary tract sepsis seemed most likely, so he was given a therapeutic trial of intravenous cefuroxime. Three hours after the first dose, he had a severe rigor, tachycardia and temperature of 38°C. He became apyrexial the following day and the liver function tests progressively improved thereafter. During immunological tests an abnormal fluorescence pattern was obtained which prompted a Venereal Disease Reference Laboratory (VDRL) slide test. This proved positive in high titre (>1 : 2048), hence full serological tests for syphilis were undertaken: *Treponema pallidum* haemagglutination test (TPHA) positive >1 : 20,400, fluorescent treponemal antibody absorbed test for IgG (FTA-ABS IgG) positive, FTA-ABS IgM positive. He was referred to the department of Genito-urinary Medicine where a history of gonorrhoea 6 years before was obtained but sexual abstinence during the 4 years before admission was maintained. On examination he had patchy balanitis and pediculosis pubis. Darkground examination of material from the subpreputial area failed to demonstrate *Treponema pallidum*.

Based on the history of a rash, generalized lymphadenopathy, a rigor after a treponemocidal antimicrobial and the serological results, a presumptive diagnosis of secondary syphilis was made. He was treated with intramuscular procaine penicillin 600,000 IU daily for 14 days and showed a satisfactory serological response: VDRL 1 : 64, TPHA 1 : 1280, FTA-ABS IgG positive, FTA-ABS IgM negative 3 months after treatment. The nephrotic syndrome had completely resolved with normal serum albumin and 24 hour urinary protein concentrations. A human immuno-deficiency virus type 1 (HIV-1) antibody test performed with his consent proved negative. Shortly before leaving hospital, he admitted to sexual contact with a prostitute about 6 months before admission.

Discussion

This patient was eventually diagnosed as having nephrotic syndrome due to syphilitic membranous glomerulonephritis and syphilitic hepatitis.

The prevalence of nephrotic syndrome in early syphilis was reported as 0.28% in one large series[3] and it is typically an acute-onset, self-limiting phenomenon. Since the development of immunofluorescent staining techniques, the renal lesion has been clearly shown to be an immune-complex glomerulonephritis[4,5] similar to early membranous glomerulonephritis as demonstrated in this case.

Clinically apparent syphilitic hepatitis has a similar incidence – 0.24% in the large retrospective study of Hahn[6] – but subclinical involvement may be more common.[7] Most reports agree that the alkaline phosphatase is disproportionately raised in relation to serum bilirubin and transaminases but no specific pattern of histological change has been described and the pathogenesis remains unclear.[8]

The antimitochondrial antibody detection in our patient showed an immunofluorescent pattern distinct from that of primary biliary cirrhosis which, if recognized, may be useful in the diagnosis of early syphilis (Swana, G, personal communication). The antimitochondrial test was negative 3 months after treatment. This case also reiterates the importance of serological tests for syphilis in the investigation of nephrotic syndrome and that the presence of one sexually-transmitted disease, such as pediculosis in this case, should always prompt looking for others.

Acknowledgements

We thank Dr D.R. Davies, Consultant Histopathologist for his advice in the interpretation of the renal biopsy specimens.

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