Circulating immune complexes in syphilitic nephropathy

A case report

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SUMMARY A case of transient nephrotic syndrome caused by secondary syphilis is described. A renal biopsy was performed revealing subepithelial hump-like electron-dense deposits and fusion of epithelial foot-processes. Complement C1q-binding-activity and anticomplementarity were demonstrated in the blood, indicating the presence of circulating immune complexes. This strongly suggests that circulating immune complexes are significant in the immunopathogenesis of syphilitic nephropathy.

Introduction

Although rare, secondary syphilis can be associated with kidney disease. In 1040 syphilitic patients proteinuria was found in 7.1% of them (Herman and Marr, 1935) and nephrotic syndrome appeared in 0.3%. Haemorrhagic nephritis has also been described (Thomas and Schur, 1946; Bhorade *et al.*, 1971). Impairment of renal function in secondary syphilis is usually transient with complete resolution either spontaneously or after penicillin treatment. Studies employing electron microscopy and immunofluorescent techniques have demonstrated immune complex deposits on the glomerular basement membrane in syphilitic nephropathy (Falls *et al.*, 1965; Braunstein *et al.*, 1970; Bhorade *et al.*, 1971; Hellier *et al.*, 1971; Kaplan *et al.*, 1972; Yuceoglu *et al.*, 1974). These, together with other studies (Gamble and Reardan, 1975; Tourville *et al.*, 1976), strongly suggest that circulating immune complexes are a pathogenetic factor in the clinical pattern of secondary syphilis. We report a case of secondary syphilis presenting as a nephrotic syndrome in which a kidney biopsy showed deposits in the glomeruli indicating an immune complex nephritis.

Investigation of serum samples from the patient revealed that circulating immune complexes were present. To our knowledge this has not previously been demonstrated in syphilitic nephropathy.

Case report

A 37-year-old woman was admitted to the Department of Medicine C, Aarhus Kommunehospital, Denmark in July 1976. The patient's symptoms had started three weeks before with arthralgia, lethargy, headache, and vomiting. Ten days before admission to hospital the patient developed generalised oedema, and five days later a papular eruption on the trunk as well as on the palms of the hands and soles of the feet. On admission examination of the heart, lungs, and abdomen was normal. Blood pressure was normal during the entire admission.

Laboratory findings revealed heavy proteinuria of about 10 g a day. Investigation of the urinary sediment showed haematuria with 10-20 erythrocytes and 2-5 leucocytes per high-powered field, and numerous hyaline casts and fat bodies. No erythrocyte casts were present. Blood urea: 49 mg/100 ml (8.1 mmol/l), serum creatinine: 1.2 mg/100 ml (106.1 μ mol/l) and creatinine clearance: 60-70 ml/min. Blood electrolytes and total CO₂ were normal. Total serum protein was 4.9 g/100 ml (49 g/l), serum albumin 1.8 g/100 ml (18 g/l), serum cholesterol 286-328 mg/100 ml (7.4-8.4 mmol/l), and sedimentation rate 126 mm/h. The patient was anaemic with a haematocrit value of 27%. Leucocyte and platelet counts were normal. Alkaline phosphatase was elevated: 348 units/l (normal value below 220 units/l). Bilirubin and serum aspartate aminotransferase (SGOT) were normal. Rose-Waaler test and lupus erythematosus-factor gave negative results. No β -haemolytic streptococci or other pathogenic micro-organisms were present in

throat or urine cultures. Electrocardiogram, chest x-ray, and intravenous pyelography were normal.

The Wassermann reaction was positive: 1:12, the Kahn reaction was positive 1:8, Meinicke's reaction strongly positive, and the *Treponema pallidum* immobilisation test was also positive. A Wassermann reaction performed one year earlier had been negative. Percutaneous renal biopsy was performed one week after admission before treatment with procaine penicillin retard 600 000 units a day (PAM). The clinical course is shown in Fig. 1. The nephrotic syndrome, already in partial remission before treatment, disappeared completely. The patient left hospital after three weeks without any signs of oedema and with normal kidney function and no proteinuria.

Fig. 1 The clinical course of the 37-year-old woman.

Materials and methods

Immune complexes in blood were determined by complement C1q-binding-activity (C1q-BA) (Nydegger *et al.*, 1974; Sølling *et al.*, 1978) and by an anticomplementary method modified after Mowbray (Mowbray *et al.*, 1973; Sølling *et al.*, 1978). Normal value for C1q-BA was below 15% precipitation.

The complement components C1q, C4, C3, and C3PA were determined by single radial immune diffusion according to the method of Mancini *et al.* (1965). Antibodies and protein standards for C4, C3, and C3PA from Behringwerke were used. Serum from a healthy donor was used as reference for all C1q measurements.

The percutaneous renal biopsy specimen measuring 45 mm was divided into three portions. One was fixed in Carnoy's solution and embedded in paraffin for light microscopy. Another, for electron microscopy, was fixed in 3% glutaraldehyde, postfixed in osmic tetroxide, and embedded in Vestopal W staining on the block by lead citrate and uranyl acetate. The third part was prepared for immunofluorescence, but this specimen did not contain any glomeruli.

Results

Before treatment the serum complement C1q and C4 were slightly elevated and C3 and C3PA normal. Thus no complement consumption was demonstrated. During treatment with PAM only small variations in serum complement were seen. After treatment the complement fractions declined to normal values (Fig. 2).

Fig. 2 The results of measurements of serum C1q, C4, C3, and C3PA complement and the results of measurements of immune complexes with the anti-complementary assay and C1q-BA.

The anticomplementary assay was positive before and the day after penicillin treatment was initiated. During treatment large fluctuations in C1q-BA were seen with normal and elevated values. After treatment the C1q-BA was normal (Fig. 2).

The biopsy specimen prepared for light microscopical examination contained 35 glomeruli. All were normal without any hypercellularity. The mean

glomerular cell count (all three cell types) was 120 per cross-section, which is within 95% confidence limits in our normal material. The capillary walls were thin and regular without spikes. There was no mesangial widening and no adhesions. Tubules, vessels, interstitium, and medulla were also normal. Total glomerular cross-sections from three glomeruli were investigated by electron microscopical exami-

Fig. 3 Electron micrographs from glomerular capillary wall. Several accumulations of electron dense deposits (humps) are situated subepithelially (arrows) (a) $\times 12000$; (b) $\times 33600$.

EP=visceral epithelial cell; CAP=capillary lumen; EN=endothelial cell; BM=basement membrane.

nation together with several selected fields at larger magnification. In all glomeruli a multitude of hump-like subepithelial dense deposits were seen on the capillary basement membrane (Fig. 3). The epithelial foot processes were fused (retracted) and there was a severe villus-like degeneration of epithelial cells.

Discussion

The generally accepted criteria for diagnosing syphilitic nephropathy, as specified by Bhorade *et al.* (1971), were found in our patient: the clinical picture of secondary syphilis, an elevation of Wassermann reaction titre from 0 to 12 as an indication of recent infection, spontaneous remission of the nephrotic syndrome accelerated by penicillin, and no signs of other renal disease.

When C1q-binding-activity (C1q-BA) and anti-complementarity (AC) can be demonstrated, circulating immune complexes are generally accepted as being present (Mowbray *et al.*, 1973; Nydegger *et al.*, 1974). The simultaneous demonstration of C1q-BA, AC, and dense deposits in glomeruli strongly suggest that circulating immune complexes are a pathogenic factor in syphilitic nephropathy. Similar findings have been described in systemic lupus erythematosus (Nydegger *et al.*, 1974; Johnson *et al.*, 1975), but not previously in syphilis. Circulating immune complexes may also be of pathogenic importance in the liver and skin lesions of secondary syphilis (Hahn, 1943). Our patient showed a slightly elevated alkaline phosphatase remitting to normal after penicillin treatment.

Determination of C1q-BA and AC started on the eighth day after admission, 18 days after appearance of the patient's oedema. Consequently we cannot demonstrate any relationship between C1q-BA, AC, and the presence of proteinuria.

Remarkably large variations in C1q-BA and AC were observed during the period of penicillin treatment. An explanation might be that irregular lysis of the treponemes as a result of the penicillin gave rise to fluctuating levels of antigen-antibody complexes. Another possibility is that immune complexes might be present only intermittently in the circulation (Agnello *et al.*, 1976). The latter suggestion is supported by the fact that immune complexes can be detected only in a certain percentage of patients with diseases such as systemic lupus erythematosus, in which immune complexes are thought to be important.

Serum complement was normal or slightly elevated. At the start of penicillin treatment, a temporary decrease in complement was observed. Similar findings have been reported by Fulford *et al.* (1976) who observed a decrease during the first

hours after administration of penicillin, correlating with the appearance of the Jarisch-Herxheimer reaction. No Jarisch-Herxheimer reaction was observed in our patient.

In antibody elution studies performed on kidney biopsy material, Gamble *et al.* (1975) have demonstrated the presence of antitreponemal antibody within the glomerular deposits. Using an indirect fluorescent antibody technique, Tourville *et al.* (1976) demonstrated the presence of treponemal antigen in the glomerular deposits. The present study supports both these reports that syphilitic nephropathy is caused by circulating immune complexes.

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