Case report

Membranous glomerulonephritis in rheumatoid arthritis unassociated with gold or penicillamine treatment

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SUMMARY A 16 year old girl with rheumatoid arthritis who had not received gold or penicillamine developed a nephrotic syndrome. Her renal biopsy specimen showed membranous glomerulonephritis by light, electron, and immunofluorescence microscopy.

Key words: nephrotic syndrome, subepithelial deposit(s), electron microscopy.

Gold^{1 2} or penicillamine^{3 4} treatment is well recognised to produce membranous glomerulonephritis (MGN) in patients with rheumatoid arthritis. MGN, however, is quite rare in the absence of administration of these drugs. It has recently been suggested that MGN is associated with rheumatoid arthritis independently of drug treatment,⁵ but others argue that this is unlikely.⁶

We report a patient with MGN arising in rheumatoid arthritis without gold or penicillamine treatment.

Case report

A 16 year old girl was admitted to hospital on 9 September 1985 with heavy proteinuria and oedema. When evaluated at another hospital two years earlier she had had a strongly positive rheumatoid factor test and complained of migratory polyarthralgia. She had been diagnosed as having rheumatoid arthritis and was treated with aspirin and indomethacin, later changed to sulindac. She had first experienced facial oedema and proteinuria in April 1985. Thereafter she received oriental medicines and regular injections of methylprednisolone acetate intramuscularly once a week. Gold or

penicillamine had never been given before the admission.

Physical examination showed anasarca and weight 12 kg more than her usual. She had morning stiffness for up to two hours and also had joint pain in the hands, elbows, and feet, and reduced range of motion of the right elbow with swelling. Radiographs showed no destructive lesion in the affected joints.

Laboratory studies showed a high sedimentation rate of 170 mm/h, haemoglobin 104 g/l, normal white blood cell count, and thrombocytes. Total serum proteins were 46 g/l, albumins 30.9% (14 g/l), α_1 globulins 3.5%, α_2 globulins 42.2%, β globulins 13.0%, γ globulins 10.5%. Blood urea nitrogen was 11.4 mmol/l, serum creatinine 61.9 μ mol/l, Na⁺ 138 mmol/l, K⁺ 3.8 mmol/l, Ca²⁺ 2 mmol/l, U²⁺ 1.1 mmol/l. Serum aspartate transaminase was 11 U, alanine transaminase 5 U, alkaline phosphatase 7.4 KAU, cholesterol 12.6 mmol/l, triglycerides 3.8 mmol/l, uric acid 0.25 mmol/l. Antistreptolysin O titre was 80. Lupus erythematosus test was negative. Latex test for rheumatoid factor was strongly positive, anti-DNA antibodies negative. C₃ was 680 mg/l, C₄ 130 mg/l. IgG 2.08 g/l, IgA 3.41 g/l, IgM 3.67 g/l. Hepatitis B surface (HBs) antigen, anti-HBs-antibodies, and a serological test for syphilis were all negative.

A 24 hour urine specimen contained 13 g protein with calculated creatinine clearance

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Fig. 1 Electron micrograph of the first renal biopsy specimen. Electron dense deposits are present in subepithelial sites with irregularity of the basement membrane.

55.0 ml/min. The sediment showed 5–10 red blood cells and white blood cells, and occasional granular casts per high power field.

The first renal tissue obtained on 9 October 1985 had few glomeruli, which were visible only in the Epon embedded material. Electron microscopy showed podocyte effacement. The glomerular basement membrane was thickened in a segmental pattern with subepithelial deposits (Fig. 1). There were no dense deposits in the mesangium.

The second renal biopsy performed seven months after the first one had 20 glomeruli. Optical microscopy showed neither cellular proliferation nor increase in the mesangial matrix. Focal tubular atrophy was present, accompanied by slight fibrosis. Immunofluorescence was strongly positive with IgG in a granular pattern, negative with IgA, and weakly positive with C3 and IgM along segmental loops. Electron microscopy showed irregularity of the basement membrane with subepithelial deposits of varying density, lucent areas, and thinner 'spikes' than previously.

Discussion

A diagnosis of rheumatoid arthritis in this patient was 'definite' by clinical and serological criteria,⁷ and membranous glomerulonephritis was proved by renal biopsy. The patient had received aspirin, indomethacin, sulindac, oriental medicines, and injections of methylprednisolone, but never gold or

penicillamine. Though it is reported that non-steroidal anti-inflammatory drugs induce lipoid nephrosis and interstitial nephritis,^{8,9} none of the administered drugs is known to cause MGN.

Recent studies of biopsy tissue have shown a variety of pathological changes in patients with rheumatoid arthritis. Mesangial alterations consisting of increased matrix or hypercellularity, or both, are most common, whereas MGN is distinctly rare in the absence of gold or penicillamine treatment. This lesion was not found in the studies by Salomon *et al.*,¹⁰ Hordon *et al.*,¹¹ or Sellars *et al.*,⁶ except related to gold or penicillamine treatment. Samuels *et al.* reported eight patients with rheumatoid arthritis, two of whom had not received gold or penicillamine, and suggested that MGN was a feature of rheumatoid disease.⁵ Sellars *et al.*, however, point out the possibility of overlap with lupus erythematosus because of positive antinuclear factors (ANF).⁶ MGN with positive ANF was seen in a patient studied by Friedman *et al.*¹² In our case also there is a possibility of lupus because of the fact that some patients with apparently idiopathic MGN may later develop the full syndrome of lupus, and the fact that not all patients with lupus have a positive ANF.

There are a few reports in which MGN occurred in a patient with rheumatoid arthritis not treated with gold or penicillamine. Row *et al.* described a patient with rheumatoid arthritis in whom MGN onset was unrelated to ingestion of non-steroidal anti-inflammatory drugs.¹³ Though details of treatment with gold or penicillamine were not given, MGN was also recognised in the study of Brun *et al.*¹⁴ Other reports have been made by Figueroa and Waxman¹⁵ and Evers *et al.*¹⁶

More recently Helin *et al.* reported nine rheumatoid patients with MGN, one of whom had never received gold or penicillamine.¹⁷

Although it is obscure why MGN is so rare in rheumatoid arthritis, the possibility of coincidental occurrence of idiopathic MGN and rheumatoid arthritis in patients, including our case, seems small. We support the hypothesis that rheumatoid disease is causally related to MGN.

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