Case report

Progressive proliferative glomerulonephritis in a patient with rheumatoid arthritis treated with D-penicillamine

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SUMMARY A 49 year old man with rheumatoid arthritis developed a proliferative glomerulonephritis with progressive renal impairment during treatment with D-penicillamine. His renal function continued to deteriorate after the drug was stopped but improved after treatment with corticosteroids and azathioprine.

Key words: renal failure, vasculitis, immune complexes.

Progressive renal impairment is not usually a feature of the renal lesions that may occur in patients treated with D-penicillamine.^{1,2} We report a patient with rheumatoid arthritis (RA) who developed a rapidly progressive proliferative glomerulonephritis during treatment with D-penicillamine.

Case report

A 49 year old man presented in 1981 with seropositive nodular RA. In June 1982 when his renal function and blood pressure were normal and antinuclear factor (ANF) and deoxyribose nucleic acid (DNA) binding tests negative he started treatment with D-penicillamine (250 mg daily). The dose was increased in July to 250 mg twice daily and again in October 1982 to 250 mg three times daily. Proteinuria developed in November 1982 and persisted despite stopping D-penicillamine.

By January 1983 his blood pressure had risen to 170/115 mmHg, he had two small haemorrhages in

his right optic fundus, and ankle oedema. His haemoglobin was 9.2 g/dl (92 g/l), leucocytes 6800/ μ l (6.8×10^9 /l), and erythrocyte sedimentation rate (ESR) 144 mm/1st h. Plasma urea was 10 mmol/l and creatinine 190 μ mol/l. Latex test for rheumatoid factor was strongly positive (titre greater than 1 in 320), but the ANF was only weakly positive (titre 1/5). C3 162 mg/dl (1620 mg/l)—(normal range 650–1300 mg/l) and C4 62 mg/dl (620 mg/l)—(NR 120–320 mg/l) were raised. The 24 h urinary protein was 12.5 g. An electrocardiogram (ECG) showed ischaemic changes in the lateral chest leads. Renal biopsy showed diffuse glomerular lesions with endocapillary cell swelling and occasional capsular adhesions associated with focal sclerosis and reactive extracapillary cell aggregates. In a few lesions collections of foam cells were seen within affected capillary loops, and one lesion showed localised tuft necrosis with deposited nuclear debris. Two small blood vessels were normal on light microscopy.

He was then treated with atenolol, hydralazine, spironolactone, and frusemide until his blood pressure was controlled, at which stage the hydralazine and spironolactone were stopped. During the next three months proteinuria (approx 5 g/24 h) persisted and renal function deteriorated (Fig. 1). He developed bilateral pleural effusions and widespread retinal haemorrhages despite good control of his

Accepted for publication 24 June 1985.

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Fig. 1 Changes in plasma creatinine (reciprocal linear plot) during course of patient's illness.

blood pressure. ANF titre became strongly positive (1/640), the DNA binding titre was slightly raised at 30 U/ml (NR 0–25), but the rheumatoid factor titre was unchanged. Serum C3 and C4 remained raised, and serum IgG was 188% of normal (NR 50–170 g/l), IgM 1374% (NR 50–180 g/l), and IgA 675% (NR 50–170 g/l). Immune complex assays (C1q binding, polyethylene glycol precipitation), were positive, and a skin biopsy showed a mixed perivascular and superficial infiltrate with T cells in the dermis which stained diffusely for IgG. The epidermis showed a granular basement membrane fluorescence for IgM, IgA, and C3.

In April 1983 treatment was started with prednisolone (60 mg daily), azathioprine (100 mg daily), and dipyridamole (150 mg daily). Subsequently his general condition and renal function improved (Fig. 1), and the ECG reverted to normal. Immunoglobulin and complement levels returned to normal within three months and the ANF titre fell to 1/5 by February 1984. The latex test for rheumatoid factor remained positive. The dose of prednisolone was gradually reduced and by October 1984 he was taking azathioprine (150 mg daily) and prednisolone (10 mg daily). At that time, the plasma urea was 5.6 mmol/l, plasma creatinine 121 μmol/l, and creatinine clearance 65 ml/min. There was 0.9 g proteinuria per 24 h.

Discussion

Patients with RA treated with D-penicillamine may develop proteinuria, which usually resolves when the drug is withdrawn.¹ In most cases this is due to

an immune complex mediated membranous nephropathy, which improves histologically as proteinuria diminishes and is not usually associated with progressive renal impairment.^{1–5}

Proliferative glomerulonephritis is a rare complication of treatment with D-penicillamine. It was initially described in a patient with Wilson's disease⁶ but since then has occasionally been reported in patients with RA who have either developed a drug induced systemic lupus erythematosus syndrome (SLE),⁷ necrotising vasculitis,^{8,9} or Goodpasture's syndrome.^{10–12} Rarely it has been seen in patients with RA who have not developed features of additional systemic disease.¹³ Our patient is of interest in that he developed a proliferative glomerulonephritis leading to a progressive deterioration in renal function, which continued despite stopping D-penicillamine. He had many features of systemic disease with pleural effusions, ischaemic changes on his ECG, a raised ESR, and progressive retinal lesions despite blood pressure control, but he was atypical in several respects. In contrast with the few reported cases of drug induced SLE with renal impairment^{7,14} the ANF titre was low (1/5) and complement and immunoglobulin levels were high after renal function had started to deteriorate. It has been suggested that penicillamine induced SLE unlike other drug induced forms is associated with antibody to native DNA rather than single stranded or denatured DNA¹³ and that in this respect it is similar to the nephritis associated with spontaneously occurring SLE. For this reason it is not surprising that D-penicillamine induced SLE is sometimes associated with marked elevation of the

DNA binding titre.¹⁵ In our patient we do not know whether the serological changes that subsequently occurred were due to D-penicillamine or hydralazine, but renal function had started to deteriorate and the renal biopsy was performed before treatment with hydralazine.

The widespread retinal haemorrhages that developed despite control of his blood pressure suggested a generalised vasculitis. However, he did not develop any of the cutaneous manifestations frequently described in patients with 'rheumatoid vasculitis',¹⁶ nor was there the involvement of medium sized vessels on renal biopsy that has been described in patients who have developed renal impairment with a necrotising vasculitis after treatment with D-penicillamine.^{8,9}

The outcome of the few reported cases of proliferative glomerulonephritis that have been associated with D-penicillamine has been variable. When associated with drug induced SLE⁷ a good response has been noted on withdrawal of D-penicillamine and treatment with steroids and cyclophosphamide. When associated with necrotising vasculitis the eventual outcome in those patients reported has been fatal despite treatment with steroids.^{8,9} In those cases in which acute proliferative glomerulonephritis has occurred in association with pulmonary haemorrhage but without the presence of antiglomerular basement membrane antibody, response to plasma exchange and immunosuppressive drugs has been reported,¹⁰ though other patients have progressed rapidly to end stage renal failure.¹¹

Renal function in our patient continued to deteriorate for six months after stopping D-penicillamine despite control of his blood pressure. At that stage he was given steroid therapy, azathioprine and dipyridamole, and it is probable that this played a major part in his recovery.

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