Case Report

Coexistent membranous nephropathy and ANCA-positive crescentic glomerulonephritis in association with penicillamine

P. W. Mathieson1, D. S. Peat2, A. Short1 and R. A. Watts3

Departments of 1Medicine and 2Pathology, University of Cambridge, Cambridge; and 3Department of Rheumatology, Ipswich Hospital, Ipswich, UK

Key words: ANCA; penicillamine; membranous nephropathy; systemic vasculitis

Introduction

D-penicillamine is an effective disease-modifying drug in rheumatoid arthritis, but adverse effects are common and often lead to the cessation of treatment with this agent [1]. A variety of autoimmune disorders may be induced by the drug, either associated with organ-specific autoantibodies (e.g. myasthenia gravis or pemphigus vulgaris) or with non-organ-specific autoantibodies (e.g. systemic lupus erythematosus) [2,3]. Renal injury is seen in up to 30% of patients treated with penicillamine, typically causing proteinuria without impairment of renal excretory capacity [4]. The commonest histological finding is membranous nephropathy, but in a minority of cases there will be minimal-change nephropathy or the presence of electron-dense mesangial deposits [4].

The prognosis of penicillamine nephropathy is considered generally very good, with complete resolution typically occurring when the drug is stopped, and deterioration of renal function being exceptional. A small number of cases of crescentic glomerulonephritis associated with D-penicillamine therapy have been reported in recent years [5–7], and this may sometimes occur in the context of penicillamine-induced lupus [8]. Antineutrophil cytoplasm autoantibodies (ANCA) have been reported in one case [6]. We report a patient who developed proteinuria whilst taking D-penicillamine for rheumatoid arthritis. Proteinuria increased despite a reduction in penicillamine dosage, and he subsequently developed rapidly progressive renal failure associated with circulating ANCA. Renal biopsy showed both membranous nephropathy and a necrotizing crescentic glomerulonephritis. Despite intensive immunosuppression he subsequently developed full-blown systemic vasculitis.

Case report

Case history

The patient, a white male, was given a diagnosis of rheumatoid arthritis in 1980 at the age of 39 years after typical joint symptoms of 3 years’ duration, with rheumatoid nodules on both elbows, radiological erosions, and a strongly positive rheumatoid factor. Initially he was treated with non-steroidal anti-inflammatory drugs, but in February 1989 he was started on D-penicillamine because of inadequate control of the arthritis. The drug was introduced at 250 mg daily, increasing after 6 months to 500 mg daily. There was an excellent effect on his arthritis, and complete resolution of the rheumatoid nodules. Urinalysis and full blood counts were monitored monthly and remained normal until April 1994. At that time proteinuria (+ on dipstick analysis) was first noted. In May 1994 proteinuria persisted: 24-h urine protein excretion was 1.66 g. Blood pressure was 150/80 mmHg. Plasma creatinine concentration at this time was 81 μmol/l, a midstream specimen of urine showed no abnormality, and full blood count was normal. Penicillamine was continued at a reduced dosage (250 mg daily) for a further month. In June 1994, 24-h urine protein excretion had increased to 2.7 g and penicillamine was stopped. Two weeks later the patient became generally unwell with fever, vomiting, and malaise. Blood pressure had risen to 185/110, plasma creatinine was 324 μmol/l and he was referred to us for further investigation and management.

On admission, he was febrile (37.8°C), pale and unwell. Blood pressure was 210/115, there was no oedema and no other abnormal physical finding. Urinalysis showed ++ + + blood and ++ + + protein. Microscopy of the urinary sediment revealed numerous crenated red blood cells, numerous granular casts and a few red cell casts. Further investigations showed haemoglobin 10.4 g/dl. White blood count 11.6 x 10^9/l (neutrophils 9.51 x 10^9/l, eosinophils 0.16 x 10^9/l), platelets 352 x 10^9/l, ESR 110 mm/h, fibrinogen > 10 g/l, plasma creatinine 358 μmol/l, and C-reactive protein 110 mg/l. ELISA for antiglomerular basement

Correspondence and offprint requests to: Prof. Mathieson, Academic Renal Unit, Southmead Hospital, Bristol BS10 5NB, UK.

© 1996 European Dialysis and Transplant Association–European Renal Association
membrane (GBM) antibody was negative. ANCA was strongly positive by indirect immunofluorescence on alcohol-fixed normal human neutrophils, with a p-ANCA pattern. Subsequent antigen-specific ELISAs showed that the specificity of the ANCA was for myeloperoxidase (MPO), with no binding to either proteinase 3 or lactoferrin. Ultrasound scanning showed two normal sized, unobstructed kidneys. After control of his blood pressure, he underwent percutan-eous renal biopsy.

**Histological findings**

The renal biopsy of both cortex and medulla contained 20 glomeruli: 15 showed varying stages of focal and segmental fibrinoid necrotizing glomerulonephritis, the remaining five showed only mild and non-specific increase in cellularity. Six tufts showed proliferation of the parietal epithelial cells in Bowman’s space, with both fibrous and cellular crescents (Figure 1). Silver stain revealed cross-cut ‘spikes’ in several regions. There was much parenchymal loss and scarring with fibrosis, tubular atrophy, and diffuse, mild inflammation.

Direct immunofluorescence showed brilliant granular positivity with IgG and C3 (Figure 2) but negative staining with IgA, IgM, and Clq. Formaldehyde-fixed tissue was processed for electron-microscopy. There were numerous intramembranous immune deposits, localized to the epithelial side of the basement membrane (Figure 3). The findings were of a stage II membranous glomerulonephritis with a coexistent necrotizing crescentic glomerulonephritis.

**Management and progress**

The patient was treated with prednisolone 60 mg/day and cyclophosphamide 200 mg/day, both taken orally.

**Discussion**

This patient developed proteinuria after taking D-penicillamine for 5½ years. Patients with typical penicillamine nephropathy, usually due to membranous
of complement C4 in vivo at concentrations similar to those achieved in vitro and may impair the role of the classical pathway of complement in disposing of immune complexes. Penicillamine nephropathy, like idiopathic membranous nephropathy, is more common...
References


Received for publication. 18.9.95
Accepted: 27.9.95