

Immune complex mediated lung haemorrhage and nephritis—successful treatment with plasma exchange, haemodialysis and immunosuppressive drug therapy

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Summary

A 16-year-old boy developed an immune complex illness associated with lung haemorrhage, proliferative nephritis with crescents and renal failure. Treatment with plasma exchange, haemodialysis and immunosuppressive drugs resulted in a rapid reduction in levels of immune complexes and other mediators of inflammation and was associated with good recovery of renal and lung function. Subsequently, deterioration in renal function occurred whilst the patient was on treatment with prednisolone alone but this was reversed with a short course of plasma exchange and the addition of azathioprine. No further deterioration in renal or lung function has been observed during 18 months treatment with azathioprine and prednisolone.

Immediate plasma exchange and immunosuppressive drug treatment have been recommended for Goodpasture's syndrome. Immune complex mediated lung haemorrhage and nephritis is the main clinical differential diagnosis. Our case suggests that the same treatment is effective for both conditions if given early, and that detailed renal and immunological investigations should not be allowed to delay this.

KEY WORDS: glomerulonephritis, lung haemorrhage, immune complexes.

Introduction

Haemoptysis is uncommon in renal failure; once fluid overload and pulmonary infection have been excluded the most likely cause is antiglomerular basement membrane (anti-GBM) disease with an associated proliferative nephritis with crescents (Schwartz *et al.*, 1977). It is this condition that is now known as Goodpasture's syndrome whereas before the introduction of immunological studies this eponym was applied to all cases of lung haemorrhage and nephritis (Martinez and Kohler, 1971). More

rarely the association of pulmonary and renal disease occurs in so-called connective tissue diseases. There are well documented cases complicating systemic lupus erythematosus (Eagen *et al.*, 1978), Wegener's granulomatosis (Fauci and Wolff, 1973; Lockwood *et al.*, 1977), essential cryoglobulinaemia (Martinez and Kohler, 1971) and possibly polyarteritis nodosa (Rose and Spencer, 1957), whilst some cases defy simple classification (Loughlin *et al.*, 1978; Clinico-pathological Conference, 1973). Deposition of immune complexes is thought to play a major role in the pathogenesis of these conditions.

Before long-term dialysis became widely available only about 10% of patients with lung haemorrhage complicating nephritis survived (Duncan *et al.*, 1965). With various combinations of immunosuppressive drug treatment, bilateral nephrectomy, long-term dialysis and renal transplantation, Wilson and Dixon (1973) reported long-term survival in 15 of 32 patients with Goodpasture's syndrome, although only four of them survived without permanent renal replacement therapy. However, since the introduction of combined plasma exchange and immunosuppressive drug treatment, the morbidity and mortality of patients with anti-GBM disease has fallen even further (Kincaid-Smith and d'Apice, 1978), with claims for the effectiveness of this treatment in controlling lung haemorrhage which is the major cause of death (Lockwood, 1981).

Early plasma exchange should also be effective in patients with lung haemorrhage and nephritis not due to anti-GBM disease as it enables rapid removal of immune complexes and other mediators of inflammation, such as fibrinogen and complement, whilst the more delayed effects of immunosuppressive drug therapy are developing. We report such a patient, in whom early plasma exchange and immunosuppressive treatment led to a brisk fall in serum immune complexes, fibrinogen and complement, which was

associated with a dramatic improvement in renal and lung function.

Case report

A 16-year-old schoolboy was well until 8 weeks before admission when he developed a migrating asymmetrical arthritis affecting both small and large joints. Two weeks before admission he was referred to another hospital. No abnormality was found on examination but routine urinalysis detected blood and protein. Haemoglobin was 14 g/dl and plasma urea, electrolytes and creatinine were normal. Following this visit, and with no specific treatment, there were no further joint problems. However, his general condition deteriorated and he became anorexic. Two days before admission he coughed up a small amount of blood and became increasingly short of breath. He noticed he was passing less urine and that it was dark and frothy. He was admitted to hospital where his haemoglobin was found to be 9 g/dl and the plasma urea 25.9 mmol/litre.

He was transferred to the London Hospital on the following day, when he was pale, febrile and tachypnoeic but not cyanosed. There was axillary and inguinal lymphadenopathy and mild facial inflammation but no focal chest signs and no evidence of cardiac failure. The blood pressure was 120/80 mmHg and the urine output in the first 24 hr was 1320 ml.

Investigations showed moderate blood and protein on urinalysis; red cells and granular casts on urine microscopy; haemoglobin 6.0 g/dl; ESR 139 mm/hr; mild thrombocytopenia and burr cells on blood film; a clotting screen consistent with a diagnosis of disseminated intravascular coagulation; plasma sodium 129 mmol/litre, potassium 4.6 mmol/litre, bicarbonate 18 mmol/litre, urea 30.1 mmol/litre and creatinine 609 μ mol/litre; plasma albumin 30 g/litre, globulins 33 g/litre with normal electrophoresis; total bilirubin 24 μ mol/litre; arterial pH normal, P_{aO_2} 9.76 kPa and P_{aCO_2} 4.6 kPa. There was extensive patchy shadowing in both lung fields on chest X-ray. Sinus X-rays were normal. Lung function studies showed no airways obstruction or restriction but the corrected transfer factor was 211% of predicted and the corrected diffusing capacity of carbon monoxide (KCO) 255% of predicted. A high dose intravenous urogram showed poor concentration of the contrast medium with enlarged kidneys and distension of the pelvicalyceal system on the right but no obstruction was seen on retrograde pyelography. Anti-GBM antibodies were absent. Results of other immunological investigations which became available after the start of treatment included negative autoantibody screen, absent cryoglobulins, anti-streptolysin 0 titre <50 iu; latex titre >1:320; sheep cell agglutination

test (S.C.A.T.) titre 1:256; positive test for immune complexes (CIq binding 36%, upper limit of normal 10%). Complement and fibrinogen levels were normal. Culture of throat swabs and urine were negative.

Plasma exchange was performed 36 hr after admission to hospital using a continuous flow system (Aminco Celltrifuge) exchanging 4 litres per procedure with 0.9% saline, haemacel and plasma protein fraction containing calcium and appropriate potassium supplements. Drug treatment with cyclophosphamide (150 mg/day) and prednisolone (60 mg/day) was commenced. Plasma exchange and haemodialysis were continued daily for 1 week and on alternate days for a further week. Blood transfusion was given on dialysis to keep the haemoglobin above 6 g/dl. By the 4th day of treatment immune complexes were no longer detectable in the serum and plasma fibrinogen and complement had fallen to subnormal levels.

Serial recordings of KCO showed no evidence of further intra-alveolar haemorrhage and there was a dramatic improvement in renal function after 2 weeks of treatment. A renal biopsy was performed during the 3rd week which showed a focal segmental proliferative glomerulonephritis with crescent formation in two out of the nine glomeruli biopsied and some glomeruli segmentally or globally sclerosed. Immunofluorescence revealed a granular pattern of deposition of IgM and C3, mainly on glomerular capillary loops and deposits of fibrin within capsular crescents.

All symptoms and abnormal physical signs resolved whilst the patient was on immunosuppressive treatment. The prednisolone dose was tapered to zero over a period of 8 weeks at which time cyclophosphamide was stopped. He remained well for the next 2 months although moderate hypertension developed requiring treatment with a thiazide and beta-blocker. He was then readmitted with a brief history of polyarthralgia and recurrent episcleritis. Investigations showed no change except that the rheumatoid factor was again detectable in the serum with the S.C.A.T. positive 1:64 and latex test positive 1:80. A repeat renal biopsy showed scarring but no evidence of active inflammation (abnormalities of urine analysis had persisted throughout).

Prednisolone in a dose of 40 mg/day was re-started with improvement in his symptoms but over the next 2 weeks there was a rapid deterioration in renal function with creatinine clearance falling from 87 to 31 ml/min and plasma creatinine rising from 119 to 324 μ mol/litre. Blood pressure was well controlled during this period and there were no significant symptoms or signs. Investigations showed no evidence of further intra-aveolar haemorrhage but the S.C.A.T. was now 1:256 and the latex test >1:320 and immune complexes were again detected (poly-

ethylene glycol gelation). A further four plasma exchanges and the addition of azathioprine (100 mg/day) to the steroid treatment were followed by steady improvement in renal function. Eighteen months later he remains well on a small maintenance dose of azathioprine and prednisolone and with a creatinine clearance of 64 ml/min. Abnormalities of urinalysis persist and hypertension is controlled on triple therapy.

Discussion

This case was unusual in that disease activity was associated with the presence of circulating immune complexes and rheumatoid factor in the blood and the renal biopsy specimens suggested that deposition of immune complexes was the cause of the crescentic nephritis. The biopsy immunofluorescent patterns, as well as the negative tests for circulating anti-GBM antibody excluded the diagnosis of Goodpasture's syndrome, but lung haemorrhage at the time of the first admission was suggested by the history of increasing dyspnoea, the precipitous fall in the haemoglobin and the chest X-ray appearances. The abnormalities in KCO confirmed this suspicion (Ewan *et al.*, 1976). Subsequently, immunological tests made the diagnoses of systemic lupus erythematosus and essential cryoglobulinaemia untenable and although a vasculitis was suspected, no evidence of arteritis or granuloma formation was found in the renal biopsy specimens.

Plasma exchange has been combined with immunosuppressive drug therapy in the treatment of anti-GBM disease as a means of rapidly removing the probably toxic agent (anti-GBM antibody) as well as other mediators of inflammation such as fibrinogen and complement (Lockwood *et al.*, 1976). This regime is now established as the treatment of choice for Goodpasture's syndrome but the results of its use in rapidly progressive crescentic nephritis from other causes have been less decisive (Kincaid-Smith and d'Apice 1978). Immune complexes are frequently found in this heterogenous group of disorders and are thought to play a major role in their pathogenesis: the experimental production of immune complexes has been associated with the development of both glomerulonephritis (Fish and Michael, 1979) and lung haemorrhage (Brentjens *et al.*, 1974). Plasma exchange leads to more rapid reduction in circulating immune complexes than conventional immunosuppressive therapy (Lockwood *et al.*, 1979) and its early use in our case seemed justified as fulminating lung haemorrhage threatened immediate survival. The treatment rapidly reduced levels of immune complexes, complement, rheumatoid factor and fibrinogen. Steroid given by itself did not prevent rapid deterioration in renal function during the second

admission but the combination of steroid, plasma exchange and cyclophosphamide or azathioprine produced dramatic clinical and functional improvement during initial illness and relapse.

Reports of collected series suggest that the prognosis for the renal recovery in patients with Goodpasture's syndrome is related to the degree of renal impairment at the start of treatment (Lockwood, 1981). The corollary is that time-consuming tests may adversely affect outcome.

Unfortunately, early renal biopsy inevitably delays treatment with plasma exchange because of the risk of haemorrhage. We suggest that early treatment with plasma exchange, steroid and immunosuppressive agents should not be withheld pending detailed histological and immunological investigations in patients with lung haemorrhage and acute nephritis.

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