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CASE REPORT

Progressive renal disease despite immunosuppressive therapy in a patient with Wegener's granulomatosis

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ABSTRACT

We present a patient with Morbus Wegener and crescentic glomerulonephritis. Treatment with cyclophosphamide and prednisolone resulted in the disappearance of signs and symptoms of systemic inflammation. However, renal function deteriorated. Renal biopsy showed evidence of continuing capillary necrosis. Renal function improved with added plasmapheresis treatment. This case report illustrates that in patients with vasculitis necrotizing glomerulonephritis may remain active despite immunosuppressive therapy, even in the absence of extrarenal disease activity.

KEYWORDS

Crescentic glomerulonephritis, M. Wegener, vasculitis

INTRODUCTION

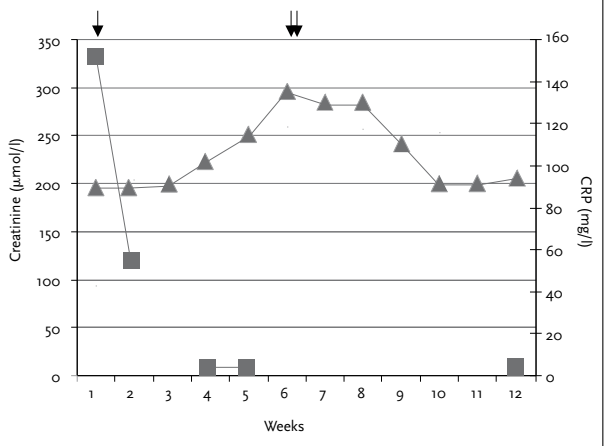
Wegener's granulomatosis is a rare disease characterised by a small vessel vasculitis in which classically the upper respiratory system, the lungs and the kidneys are involved. Renal involvement typically presents as a rapidly progressive glomerulonephritis with high morbidity and mortality.[1] Immunosuppressive therapy, if started early in the course of the disease, has improved the clinical outcome.[2] Antineutrophil cytoplasmic antibodies (ANCA) have become a valuable tool in the diagnosis of the vasculitides. A majority of patients with Wegener's granulomatosis show positive cytoplasmic ANCAs (cANCAs), which are directed against proteinase 3, a constituent of the azurophilic granules in the leucocyte. A minority of patients have antimyeloperoxidase antibodies, which provide a perinuclear ANCA staining pattern on immunofluorescence (pANCA) or even no ANCA.[3] The presence of cANCAs in a patient with upper respiratory tract symptoms and a nephritic syndrome may justify the start of immunosuppressive therapy without confirmation of glomerulonephritis by biopsy. However, a renal biopsy may be invaluable to monitor renal disease activity during treatment.

CASE REPORT

A 65-year-old male was seen three years earlier by an ear-nose-throat specialist because of extensive crusts in the nose with nasal catarrh. A biopsy specimen showed inflammation without granulomas. No specific therapy was provided. Two years later he had developed a saddle nose deformity and was referred to an internist. He had no symptoms, especially no fever, weight loss, dyspnoea or coughing. On examination he was 1.76 meter in height, 79 kg in weight and healthy looking. Further examination was unremarkable, except for the saddle nose deformation. Serum creatinine was 85 µmol/l, C-reactive protein was negative, and haemoglobin and lactate dehyrogenase (LDH) were within the normal range. ANCA was positive with a cytoplasmic pattern on immunofluorescense and positive in ELISA against proteinase 3. Urinalysis was unremarkable. Because of the apparent inactivity of the disease no specific treatment was instituted. One year later he presented with arthralgias, malaise and nose bleeding. There were no pulmonary symptoms. This time his blood pressure was elevated (180/90 mmHg) with a pulse of 90

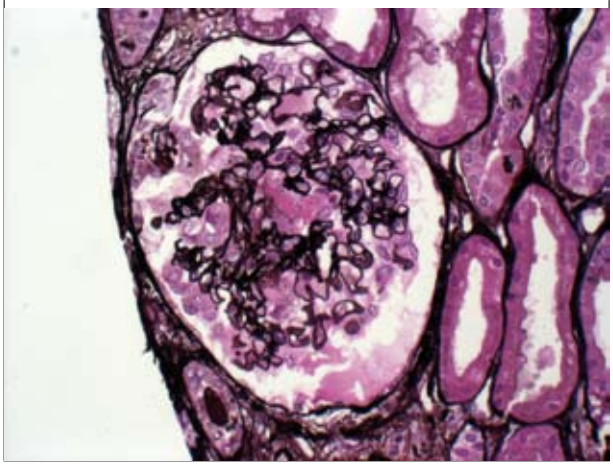
beats/min; he had blood in his nostrils and his left eye showed a conjunctivitis. Laboratory findings showed a normocytic anaemia (Hb 6.6 mmol/l), a raised creatinine of 195 µmol/l and C-reactive protein of 140 mg/l. The alkaline phosphatase was 237 U/l, the LDH 466 U/l and cANCA was positive in a titre of 16. Urinalysis showed red blood cell casts. The chest X-ray was unremarkable. A nose biopsy revealed nonspecific inflammation without granulomas. Active Wegener's granulomatosis was diagnosed and therapy was started, consisting of oral prednisolone 60 mg/day, cyclophosphamide 150 mg/day and trimethoprim-sulphamethoxazole (1:5) 480 mg/day (*Pneumocystis carinii* prophylaxis). His symptoms improved and laboratory parameters such as C-reactive protein, alkaline phosphatase and LDH normalised. In contrast, his renal function deteriorated (*figure 1*). Urinalysis showed red blood cell casts. The initial increase in serum creatinine was considered compatible with inhibition of tubular secretion of creatinine by trimethoprim, but the continuing rise prompted a renal biopsy six weeks after the start of therapy. The renal biopsy showed many glomeruli with fibrosing lesions such as fibrous and fibrocellular crescents. However, one glomerulus showed a recent capillary wall necrotising lesion characterised by an interruption of the glomerular basement membrane and fibrinous exudate in Bowman's space (*figure 2*). Because of the ongoing active renal disease plasma exchange was added to the oral therapy. Hereafter renal function improved and remained stable during follow-up (*figure 1*).

Figure 1. *Serial measurements of creatinine (triangles) and C-reactive protein (squares) before, during and after therapy*



↓Start of immunosuppressive therapy. ↓↓Start of plasma exchange (10 cycles).

Figure 2. *Glomerulus showing recent capillary wall necrosis with fibrinous exudates*



DISCUSSION

Our patient illustrates the typical presentation of Wegener's granulomatosis. Sometimes ear, nose and throat symptoms exist for years before systemic disease develops and the diagnosis is made. Our patient had nonspecific symptoms, upper respiratory symptoms and conjunctivitis. The renal manifestations with red cell casts and rapid deterioration of renal function were compatible with an extracapillary glomerulonephritis. Additionally, he developed ocular problems. Furthermore there was a normocytic anaemia, and an increased alkaline phosphatase, LDH, and C-reactive protein. Importantly cANCA with proteinase 3 specificity was present. The clinical findings in combination with the presence of the cANCA supported the conclusion that the patient was suffering from Wegener's granulomatosis. It has been established that the combination of a positive cANCA (indirect immunofluorescence) and antiproteinase 3 (ELISA) together with a systemic vasculitis provides a high sensitivity (98%) and a good specificity (73%) for Wegener's granulomatosis.[3] These specificity and sensitivity figures were used by Jennette and co-workers to estimate positive predictive values of ANCA for pauci-immune crescentic glomerulonephritis from data on more than 4000 patients who had undergone a renal biopsy. A positive ANCA in older patients (>50 years) with a rapidly progressive glomerulonephritis was extrapolated to give a positive predictive value of 99% for a pauci-immune glomerulonephritis. In elderly patients with haematuria, proteinuria and a serum creatinine between 130 to 265 µmol/l (as in our patient) the positive predictive value for a pauci-immune glomerulonephritis was 85%.[4] We felt supported by these data to start immunosuppressive therapy without performing a renal biopsy.

In our patient, the vasculitic disease activity seemed to disappear after one week of therapy. His symptoms resolved and the laboratory findings normalised except for

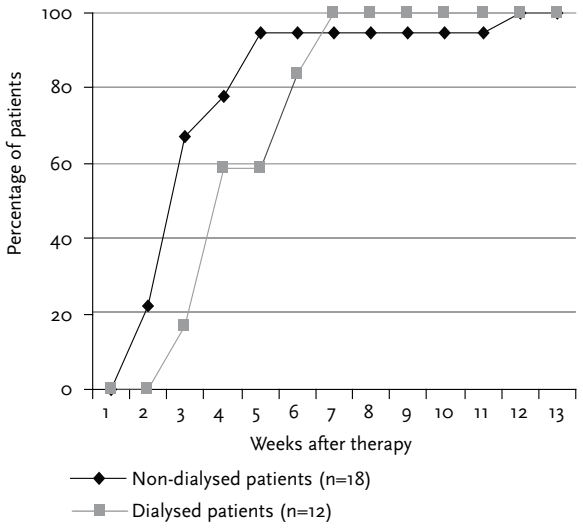
renal function. At this point we considered that the renal dysfunction could be the result of ongoing vasculitic renal activity, the effect of trimethoprim on creatinine secretion or of an intercurrent renal disease such as drug-induced tubulointerstitial nephritis. Because of his improvement in well-being and normalisation of all the other parameters we waited six weeks before performing a renal biopsy. The biopsy disclosed active glomerular cellular damage. The patient was successfully treated with ten cycles of plasma exchange. This response supports the conclusion of the biopsy and also confirms the suggested efficacy of plasma exchange when used in addition to conventional therapy in patients with severe renal disease. A pooled analysis of small studies already suggested potential benefit of plasma exchange in patients with severe renal failure.[5,6] The efficacy of plasma exchange has been proven in a recent randomised controlled trial. In this study (MEPEX) patients with ANCA-associated vasculitis and serum creatinine concentration >500 μmol/l were randomised to plasmapheresis *vs* methylprednisolone added to standard immunosuppressive therapy from the start of therapy. The results showed that renal function recovered more often in patients treated with plasma exchange than in patients treated with intravenous methylprednisolone.[7]

Reviewing our case we wondered what the optimal time for the biopsy would have been. In other words, roughly how long does it take before renal function improves after starting treatment? Therefore, we retrospectively analysed the data of our patients with biopsy-proven extracapillary proliferative glomerulonephritis treated with immunosuppressive therapy.

For the patients who responded to treatment (defined as a decrease in serum creatinine >25% or the end of dialysis treatment) we noted the time at which renal function improvement became noticeable (*figure 3*). The group of responders consisted of 14 males and 16 females with a mean age of 58 years. All patients received immunosuppressive therapy, while five patients were additionally treated with plasma exchange. Approximately one third of our patients needed dialysis treatment. In these patients a response was noted within five to six weeks, while in the nondialysed patients renal function improved within three to four weeks in all but one. Applying these results to our patient, we should have performed the biopsy no later than three weeks after starting treatment.

Obviously we cannot prove that our patient responded to plasma exchange. Our patient did not fulfil the criteria of the MEPEX study. It is not known whether renal activity is present in patients who respond to therapy, and we cannot even exclude that a later response might have occurred. However, in our retrospective study cohort all patients but one demonstrated an improvement in renal function within three weeks after starting therapy. The renal biopsy showed capillary wall necrosis, which was estimated to be less than two to three weeks old. Taken together, we felt that a wait and see policy would have increased the likelihood of more persistent kidney damage.

Figure 3. *Time to improvement of renal function after start of immunosuppressive therapy in patients with extracapillary proliferative glomerulonephritis*



In conclusion: in patients with ANCA-associated vasculitis, renal injury (necrotising glomerulonephritis) can persist despite adequate immunosuppressive therapy with prednisolone and cyclophosphamide, and should be considered even if extrarenal disease activity improves. If renal function does not improve within three weeks, a renal biopsy should be performed. In patients with vasculitis and active renal disease, addition of plasmapheresis therapy must be considered.

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