Lethal Relapse of Wegener's Disease 4 Years after Successful Kidney Transplantation

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Dear Sir,

Wegener's granulomatosis has been successfully treated with corticosteroids and cyclophosphamide, and long-term remissions have been achieved [1]. Nevertheless, 14% of the patients with renal involvement developed terminal renal failure. Kidney transplantations were performed successfully [1, 2]. Case reports on recurrence of Wegener's granulomatosis after transplantation mainly focused on vasculitis of the transplanted kidney [3-5]. We present a patient with Wegener's disease who developed a lethal relapse of the original disease 48 months after successful cadaver transplantation without involvement of the transplant.

In 1976 the 29-year-old woman developed myalgia and arthralgia of wrist joints, shoulders, knees, and feet together with erythema nodosum. One year later a scleritis was diagnosed. Treatment was started with oral methylprednisolone 12 mg/day. In January 1978 arthralgia worsened. In addition, the patient developed petechiae, purulent and haemorrhagic rhinitis, laryngitis, and haemoptysis. Chest X-ray showed fine granular confluent opacity. Proteinuria and microhaematuria were found, and the creatinine level increased up to 235 $\mu\text{mol/l}$. Renal biopsy showed an extracapillary proliferative glomerulonephritis with focal segmental capillary loop necroses. Laboratory studies did not reveal antinuclear antibodies or antibodies against the glomerular basement membrane. The clinical diagnosis was Wegener's disease involving kidney, lungs, joints, skin, eyes, and upper respiratory tract. The patient received prednisolone 20 mg/day. After a transient improvement she developed a severe haemorrhage of the lung and an acute renal failure. Artificial ventilation became necessary. The patient received five plasma exchanges, prednisolone 90 mg/day (tapering started after 2 weeks), and azathioprine 150 mg/day. Rheumatic complaints and symptoms of upper and lower respiratory tract disappeared. The chest X-ray normalized, and creatinine values fell to 230 $\mu\text{mol/l}$. In July 1978 azathioprine had to be withdrawn because of a severe pancytopenia. A relapse occurred with an increase in creatinine values, necessitating haemodialysis therapy. The patient was successfully treated with plasma exchanges, prednisolone, and cyclophosphamide 200 mg/day. Haemodialysis therapy could be stopped, and creatinine

values of 250 $\mu\text{mol/l}$ were achieved. During the following 2 years immunosuppression was complicated by repeated leukopenia and thrombocytopenia. Relapses occurred after reduction of cyclophosphamide, and the renal function deteriorated progressively. In October 1980 chronic haemodialysis was initiated. Immunosuppression was tapered and stopped. During haemodialysis therapy the patient had no signs of vasculitis reactivation. In July 1985 the patient received a kidney cadaver transplant. Prednisolone and ciclosporin were used for immunosuppression. The initial function was good, and the creatinine concentration was 168 $\mu\text{mol/l}$ at discharge. During the following 3 years the patient had transient arthralgia in knees and feet, wrist joints, and elbows. The creatinine values showed a slight increase to 200-230 $\mu\text{mol/l}$. Proteinuria was below 0.6 g/24 h, and the urine sediment was normal. In April 1989 she was again referred to our department because of myalgia and severe arthralgia of knees and shoulders, fatigue, subfebrile temperature (37.5°C), and anaemia. The haemoglobin concentration was 73 g/l. Creatinine had risen to 283 $\mu\text{mol/l}$ and urea to 43.3 mmol/l. No proteinuria was found, and the urinary sediment was normal. On admission on April 30, the patient showed a reduced general condition. During the next days she developed epistaxis, a haemorrhagic ulcerative gingivitis, sialadenitis, and swollen lymph nodes on the right side of the neck. Biopsy of a lymph node and bone marrow did not reveal a lymphoma. Serum was investigated for antineutrophil cytoplasmic autoantibodies (ANCA). The erythrocyte sedimentation rate was > 120 during the 1st. The liver enzyme

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Fig. 1. Necrotizing angitis in the lung. HE. $\times 30$.

Fig. 2. Acute inflammation of the vessel wall (submucosa of duodenum) with segmental necrosis. HE. $\times 30$.

Fig. 3. Renal transplant. No signs of vasculitis, moderate interstitial fibrosis. HE. $\times 30$. concentrations were elevated (aspartate aminotransferase 39 U/l, alanine aminotransferase 40, alkaline phosphatase 408, γ -glutamyl transpeptidase 522 U/l). The bilirubin levels rose to 268 $\mu\text{mol/l}$; cholinesterase fell to 0.97 kU/l and albumin to 24 g/l. The virus titers did not show an acute infection, and blood cultures were negative. A biopsy specimen of the renal transplant showed a moderate focal tubular atrophy, interstitial fibrosis, and a mild transplant glomerulopathy. There were no signs of vasculitis or acute rejection. As urea and potassium concentrations increased, haemodialysis treatment was started 8 days after admission. Gastrointestinal bleeding occurred, and the patient needed blood transfusions. Gastroscopy showed a severe ulcerous duodenitis. A positive c-ANCA titer of 1:64 was observed (specificity against proteinase 3 as determined retrospectively). Immunosuppression was started with methylprednisolone 500 mg i.v. and cyclophosphamide 150 mg/d i.v. Nevertheless, general condition and respiratory situation worsened dramatically. Haemoptysis occurred, and artificial respiration was necessary together with positive inotropic medication (dopamine and norepinephrine), as the blood pressure fell. Septicaemia was

suspected, and broad-spectrum antibiotic therapy was started. The patient developed respiratory failure due to a shock lung and severe pneumonia and died. Autopsy showed a necrotizing vasculitis in the lung (fig. 1) with first signs of granuloma formation which were, however, not yet typical of Wegener's granulomatosis. A purulent and haemorrhagic pneumonia was superimposed. The small intestine showed a necrotizing vasculitis with haemorrhagic infarction of the wall and widespread necrosis of mucosa and submucosa (fig. 2). No other organ had signs of vasculitis. The renal transplant was swollen with venous congestion. Histology showed a shock reaction (fig. 3). In addition, signs of a general haemorrhagic diathesis with petechiae were found, and evidence of terminal septicopyaemia (*Enterobacter cloacae* and *Pseudomonas aeruginosa*) could be demonstrated in kidney, lungs, liver, spleen, and maxillary sinuses. In this patient the diagnosis Wegener's disease was initially based on clinical symptoms and an extracapillary proliferative necrotizing glomerulonephritis. The diagnosis was confirmed by a positive c-ANCA against proteinase 3 and a necrotizing vasculitis in lungs and small intestine. No typical granuloma was found, probably due to the short course of the relapse. As the prevalence of Wegener's disease is low, only very few patients have been transplanted. Reviewing the literature [1-8], 16

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relapses in 50 patients with Wegener's disease and kidney transplantation have been reported. As all patients with relapses survived after treatment, we described a rare event: a rapid progressive and lethal recurrence of Wegener's disease after transplantation. In addition, it stresses the need for a careful short-term control of extrarenal signs of vasculitis reactivation in all organ systems, as the pattern of organ involvement may change dramatically. In this patient there was no involvement of the kidney, the organ which had the most persistent vasculitis activity before transplantation. This fact is supported by the literature [1-8], as only 50% of the patients with relapses showed a recurrence of vasculitis in the renal transplant.

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