Case Report

Relapsing Wegener’s Granulomatosis: Successful Treatment with Cyclosporin-A

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Summary We describe the case of a 32-year-old splenectomised man with severe Wegener’s granulomatosis which was refractory to conventional treatment with oral cyclophosphamide and prednisolone. Remission was temporarily induced only with plasma exchange or IV immunoglobulin. Because of frequent relapses of the disease and cyclophosphamide side effects, he was started on treatment with cyclosporin-A and a long lasting remission was achieved.

Key words Wegener’s Granulomatosis, Vasculitis, Treatment, Cyclophosphamide, Cyclosporin-A, Plasma Exchange, Immunoglobulin

INTRODUCTION

Wegener’s granulomatosis was first described in 1936. It is characterized by small vessel vasculitis affecting predominantly the upper and lower respiratory tract and the kidneys but it can also affect any organ (1). Treatment with cyclophosphamide and corticosteroids is effective in more than 90% of the cases (2,3). In this paper we describe a case of Wegener’s granulomatosis in which cyclophosphamide was not effective even at a dose of 4mg/kg/d. Remission was finally achieved with a low dose (5mg/kg) of cyclosporin-A therapy.

CASE REPORT

A 32-year-old man was admitted to our clinic on September 1991 because of fever and symptoms of multisystem disease. He had undergone splenectomy 15 years previously after an accident. On admission he was pyrexial (39°C), had mouth ulcers of 1-3cm in diameter (Fig. 1), cough with sputum production, blood in the faeces, proximal muscle weakness, arthritis of the left elbow and both ankles, palpable purpura of the buttocks, ankle and palmar regions, iridocyclitis, scleritis, purulent and bloody nasal discharge and angioedema.

Laboratory tests revealed Hb 11.3gr/dl (normal:14-18), WBC 18000/mm³ (normal 4-10X10³), platelets 611000/mm³ (140-440X10³), ESR 40mm in the 1st hour, creatinine 0.8mg% (normal 0.5-1.5), SGOT 87U/ml (normal 7-27), SGPT 43U/ml (normal 8-30), CPK 850IU/L (normal 20-134), LDH 467IU/L (normal 47-140), CRP 200mg/l (normal 0-5), RF 69U/ml (normal 0-40), circulating immune complexes measured by a Clq binding assay 8.7µg/ml (normal 0-1.5), and negative antinuclear and anti-GBM antibodies. C3 and C4 were normal, but C4 gradually fell over a period of 15 days from 0.41 to 0.11 gr/l (normal: 0.20-0.50).

The indirect immunofluorescence assay for antineutrophil cytoplasmic antibodies (ANCAs) was strongly positive (1/640) with cytoplasmic staining. ANCAs were also found positive by an a-granule specific ELISA (150 U/ml, normal range: 0-10). Urinalysis revealed microhaematuria and the 24h urine protein excretion was 450mg. The chest radiograph revealed infiltrates of the right lung without cavitation and the chest CT-scan, which was performed 10 days later, showed bilateral diffuse infiltrates (Fig. 2). The CT-scan of the sinuses showed involvement of the maxillary and sphenoid sinuses. Colonoscopy revealed some ulcers of the large intestine at a distance of 20cm from the anus. The biopsy of a skin lesion revealed leukocytoclastic vasculitis and the biopsy of an oral lesion showed vasculitis and necrosis without granuloma formation.

After his admission he developed hemoptysis, atrial fibrillation and his ECG showed depolarization abnor-
malities in the leads II, III, AVF. The diagnosis of Wegener's granulomatosis was made and he was started on prednisolone 75mg/d and cyclophosphamide 150mg/d, orally. Ten days later he developed pulmonary bleeding and he received a 3-day treatment with I.V. methylprednisolone, 1gr/d. The cyclophosphamide dose was increased to 200mg/d and the prednisolone to 125mg/d. On the following days there was an improvement but 13 days later the disease deteriorated with fever, sinusitis and urinary findings of glomerulonephritis with nephrotic syndrome: 40 red blood cells per high power field (hpf), erythrocytic, mixed and lipid casts and proteinuria (6gr/24h). The treatment was changed to prednisolone 125mg/d plus cyclophosphamide 1gr IV. The fever, the sinusitis and the constitutional symptoms improved temporarily but 12 days later the symptoms relapsed. He was again given oral cyclophosphamide 300mg/d but the disease deteriorated further and he developed fever, mononeuritis, new mouth ulcers, scleritis and active urinary sediment with urine protein up to 12gr/d. For this reason he was started on plasma exchange, one plasma volume of 3.5 lt daily for 5 consecutive days and then every other day for 8 days. This treatment proved effective and for the following two months the patient received cyclophosphamide 200mg and prednisolone 45mg/d which was reduced by 5mg every 15 days until the dose of 30mg/d and then 2.5mg every 20 days was reached.

On February 1992, he developed haemorrhagic cystitis (when the total dose of cyclophosphamide was 19gr) and the treatment was changed to cyclophosphamide 500mg IV every week plus mesna (2-mercaptoethanesulfonate). One month later he received cyclophosphamide 1gr IV in order to increase the interval between doses, but 14 days later, when the dose of prednisolone was 25mg, he developed a relapse with fever, arthralgias, epistaxis and urinary findings of glomerulonephritis. CRP was 150 mg/l and ESR 80mm in the 1st hour. Treatment was changed to cyclophosphamide 500mg IV on weekly intervals and prednisolone was increased to 40mg/d, but after a month the above manifestations of the disease remained uncontrollable. Cyclophosphamide was switched to 200mg/d orally without result and improvement was only achieved after the administration of human immunoglobulin 400mg/kg/d IV for 5 days. During the following two months cyclophosphamide at the dose of 200mg/d was enough to control the disease, but caused leukopenia (WBC < 2000), while a lower dose could not control the symptoms and the patient had a new relapse with fever, arthralgias, sinusitis, CRP 123mg/l and mild urinary sediment abnormalities (10 red cells per hpf, erythrocytic and mixed casts and proteinuria up to 500mg/24h) in the beginning of August 1992. The search for infection was negative and the symptoms did not respond to broad spectrum antibiotics. At this time the treatment was changed to cyclosporin-A 5mg/kg/d; the dose of prednisolone was not increased. One week later the symptoms resolved and the urinary sediment became normal. Two months later the dose of cyclosporin-A was reduced to 4mg/kg/d and eight months later the dose was further decreased with a rate of 50mg every two months. The duration of cyclosporin-A treatment was 19 months. During this time the patient was free of symptoms. Now, 17 months after stopping cyclosporin-A, he is taking prednisolone 2mg and cotrimoxazole and there is no evidence of relapse despite the development of a low titer of cANCA (1/40). His last serum creatinine was 1.3mg% (July 1995).

The patient, who was already severely immunocompromised, developed severe infections following the cyclosporin-A therapy. Forty days after the initiation of cyclosporin-A he developed respiratory insufficiency due to Pneumocystis carinii pneumonia, which was treated...