A case of Wegener’s granulomatosis showing a dramatic response to corticosteroid and cyclophosphamide therapy
— Evaluation of anticytoplasmic antibodies (ACPA) in serum samples —

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Key words: granuloma, combined therapy, ACPA, immunofluorescence, Wegener’s granulomatosis

Abstract

A case of Wegener’s granulomatosis with renal dysfunction is described. Granulomatous lesions of the lung, left eyelid and left leg, and chronic sinusitis were observed at the time of admission. Renal and skin biopsy specimens revealed typical features of Wegener’s granulomatosis on light microscopy and immunofluorescence microscopy. A dramatic response occurred following corticosteroid and cyclophosphamide therapy, characterized by improvement of proteinuria and renal function, and disappearance of the granulomas and $^{67}$gallium citrate accumulations in both the eyes and nose. Furthermore, the levels of anticytoplasmic antibodies (ACPA) in the serum samples were significantly decreased after such therapy. It appears that combined therapy with corticosteroid and cyclophosphamide can be effective in improving proteinuria and renal dysfunction, and in reducing of ACPA in patients with Wegener’s granulomatosis.

Introduction

Wegener’s granulomatosis is characterized by granulomatous vasculitis of the upper and lower respiratory tracts associated with glomerulonephritis. Although the pathogenesis of Wegener’s granulomatosis remains unknown, this disease is generally considered to be a hypersensitivity disorder because of the granulomas, inflammation of the small arteries and/or veins, and glomerulonephritis. Immune complexes are deposited in the glomeruli of some patients with Wegener’s granulomatosis as described by Fauci and Wolff [1]. Recently, Wundel et al. [2] suggested that a significant correlation exists between the levels of autoantibodies against neutrophil cytoplasm (anticytoplasmic antibodies; ACPA) in the sera and the disease activity in patients with Wegener’s granulomatosis.

In the present report, a case of Wegener’s granulomatosis showing a dramatic response to corticosteroid and cyclophosphamide therapy is described. The levels of ACPA in the serum samples were significantly decreased in indirect immunofluorescence after such therapy. It is suggested that combined therapy with corticosteroid and cyclophosphamide may be effective in improving the proteinuria and impaired renal function of patients with renal involvement in Wegener’s granulomatosis.

Case Report

A 51-year-old man was admitted to the Japan on for investigation of proteinuria, microhematuria, nasal bleeding and tumors of the upper part of the left eyelid and left
leg. He had been well until 6 months previously when he developed a tumorous lesion in the upper part of the left eyelid and injection of the left conjunctiva. For 20 years, he had suffered from chronic sinusitis. There was no history of liver diseases and/or vasculitis. No significant family history was noted.

On physical examination, his blood pressure was 130/80 mmHg in a supine position. There was no evidence of pretibial edema, lymphoadenopathy or purpura. Large tumors were observed in the upper part of the left eyelid and left anterior thigh, i.e. measuring 2 × 1.5 cm and 10 × 10 cm, respectively (Fig. 1a). Urinalysis was positive for blood, and the urinary sediment revealed numerous red blood cells with hyaline, granular and red blood cell casts. The 24-hour protein excretion was 2.9 g. Laboratory tests showed a hemoglobin level of 11.4 g/dl, red blood cell count of 3.74 × 10^6/μl, and white blood cell count of 11,000/μl with 87% neutrophils, 10% lymphocytes, 2% monocytes, 1% eosinophils and 0% basophils. The erythrocyte sedimentation rate (ESR) for 1 hr was 104 mm. The blood urea nitrogen (BUN) level was 15 mg/dl, the serum creatinine (s-Cr) 0.9 mg/dl, uric acid 2.4 mg/dl, serum albumin 3.4 g/dl, and total protein 7.3 g/dl. Rheumatoid factor was negative and antinuclear
or DNA antibodies were negative. Hepatitis B surface antigen was also negative. The titers of antistreptolysin O and antistreptokinase were within normal limits. The serum IgE level was 122 u/ml (normal range: <500 u/ml). The serum IgA, IgG, IgM, C3 and C4 levels were normal. The creatinine clearance (CCr) was 101 ml/min at the time of admission. The PSP test level (15 min) was 18%. The levels of beta-2 microglobulins were 2.8 mg/l in the serum (normal values: 0.8-2.4 mg/l) and 6500 μg/l in the urine (normal values: <250 μg/l), and urine NAG was 23.7 u/l (normal values: <7.0 u/l). The renal concentrating capacity was slightly diminished. A chest X-ray revealed two round shadows in the left lower lung field. Computer tomography demonstrated a tumorous lesion in the extraocular regions of the left eye. A 67gallium citrate scan showed accumulations in both eyes, kidneys and the nose (Fig. 2). No aneurysms in either kidney were detected by renal angiography.

Renal biopsy was performed without any complications on . In sections stained with hematoxylin-eosin and PAS, all glomeruli showed mild or marked mesangial hyper-
of the tumors in the left eyelid and left thigh was observed (Fig. 1b). At that time, the abnormal shadows in the left lung had disappeared completely on chest X-ray. A $^{67}$gallium citrate scan revealed no accumulation in both eyes, kidneys or the nose.

Detection of autoantibodies against neutrophil cytoplasm (anticytoplasmic antibodies; ACPA) was performed by the method of Wounde et al. [2]. Serum samples were obtained from the patient before and after 2 months of therapy. The serum samples were diluted with PBS (pH 7.2). Polymorphonuclear cells (PMN) were obtained from 2 healthy adults (medical doctors). PMN were reacted with serial dilutions of the patient's serum or healthy adults' serum at room temperature for 30 min. After brief washing with PBS, the PMN were stained with FITC-labelled rabbit anti-human
Fig. 5a. Positive reaction for ACPA in the serum sample at the time of admission (×400), 5b. ACPA was not detected after 2 months of therapy (×400).

IgG antiserum (1:40 in PBS, Behringwerke, AG, Marburg/Lahn, FRG) at room temperature for 45 min. The samples were then examined under a Zeiss Ortholux immunofluorescent microscope. A perinuclear pattern of ACPA was observed before the therapy (Fig. 5a), and the titers of ACPA before the therapy were 1:32. However, after the therapy, ACPA was not detected at all (Fig. 5b). Serum samples of healthy adults did not exhibit ACPA activity.

Discussion

Wegener’s granulomatosis is generally considered to be a form of systemic granulomatous vasculitis although the pathogenesis of this disease remains obscure. The diagnosis of this disease is based on the findings of upper and lower respiratory tract involvement, renal disease and a variable degree of disseminated vasculitis. In the present case, granulomatous lesions of the lung, left eyelid and left leg, chronic sinusitis, and renal involvement, i.e. proteinuria, urinary casts and renal dysfunction, were observed during the clinical course. The light microscopic and immunofluorescence findings of renal tissues and skin lesions of the left leg in this case were typical of Wegener’s granulomatosis. It is postulated that all these findings were due to systemic granulomatous vasculitis. Fauci et al. [3] reviewed the effect of combined therapy with cyclophosphamide and corticosteroid in 85 patients with Wegener’s granulomatosis. They reported that complete remission was achieved in 79 out of the 85 patients (93%) with this disease. In the present case, 60 mg of corticosteroid and 100 mg of cyclophosphamide per day were administered after reaching a definite diagnosis. The levels of proteinuria, urinary casts, Cr, s-Cr, urine NAG and anemia were dramatically improved after 2 months of this therapy. Furthermore, the granulomatous lesions, abnormal shadows in the left lung, and accumulation of 67gallium citrate in both eyes, kidneys and the nose also disappeared completely.

Recently, Woude et al. [2] and Lockwood et al. [4] observed a significant correlation between the levels of ACPA and the disease activity in patients with Wegener’s granulomatosis. Yoshida and Nagasawa [5] also reported that the detection of ACPA is useful for early diagnosis and monitoring of the disease activity in such patients. Although the titers of ACPA at the time of admission were 1:32, they became completely negative after 2 months of therapy in the present case.

It appears that combined therapy with corticosteroid and cyclophosphamide is useful for reduction of the autoantibodies against neutrophil
cytoplasm in serum samples of patients with Wegener's granulomatosis. It is concluded that such combined therapy may be effective in improving the proteinuria and impaired renal function of patients with renal involvement in this disease.

Acknowledgements

The authors wish to express their thanks to Professor Shiro Kira, Division of Respiratory Disease, and Professor Akira Nakajima, Department of Ophthalmology; Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113, Japan. This work was supported by a Research Grant for Designated Disease from the Ministry of Health and Welfare, Japan. Part of this study was presented at the 19th Congress of the Japanese Society of Nephrology, Tokyo on June 6, 1989.

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