Wegener's Granulomatosis with Eosinophilia

Hirofumi SHODA, Hiroko KANDA, Ryouichi TANAKA, Yoshiaki KOMAGATA,
Yoshikata MISAKI and Kazuhiko YAMAMOTO

Abstract

Wegener's granulomatosis with eosinophilia both in blood and tissue samples has been rarely reported. A 25-year-old woman developed fever, granulomatous inflammation of nasal mucosa, pulmonary hemorrhage, suprascleritis, and cutaneous vasculitis. She showed eosinophilia in blood and biopsy samples of skin, nasal mucosa, and lung. She was positive for proteinase 3-antineutrophil cytoplasmic antibody. She had no history of asthma. We diagnosed her as Wegener's granulomatosis with eosinophilia rather than Churg-Strauss syndrome. Her mucocutaneous and pulmonary lesions were successfully treated with high-dose corticosteroid and methotrexate, but her suprascleritis required pulsed cyclophosphamide. (Internal Medicine 44: 750–753, 2005)

Key words: Wegener's granulomatosis, eosinophilia, Churg-Strauss syndrome

Introduction

Wegener's granulomatosis (WG) is systemic vasculitis of the medium and small-sized arteries, as well as of the venules and arterioles. WG also involves the upper respiratory tract, lungs, and kidneys. The pathological features of WG are granulomatous inflammation around blood vessels and necrotizing vasculitis. The American College of Rheumatology (ACR) proposed the clinical criteria of WG in 1990 (1). These criteria include nasal or oral inflammation, abnormal chest radiographical findings, abnormal findings of urinary sediment, and granulomatous inflammation. Anti-neutrophil cytoplasmic antibodies (ANCA), particularly PR3-ANCA (ANCA specific for serine proteinase 3) are

closely associated with the diagnosis of WG. The presence of PR3-ANCA makes us suspect the diagnosis of WG rather than other vasculitic diseases (2).

Churg-Strauss syndrome (CSS) is another type of systemic vasculitis characterized by peripheral and tissue eosinophilia. CSS is characterized by preceding allergic diseases, marked peripheral eosinophilia, systemic vasculitis, and eosinophilic granulomatosis (3). ANCA is present in more than one-half of the patients with CSS, but almost all CSS patients have MPO-ANCA (ANCA specific for myeloperoxidase). PR3-ANCA-positive CSS has been rarely reported (4).

WG with eosinophilia in the peripheral blood and/or tissues has been rarely reported (5–7). In such a situation, it is difficult to differentiate WG from CSS. We encountered another patient with PR3-ANCA-positive granulomatous vasculitis with both peripheral blood and tissue eosinophilia. In this paper, we discuss the differential diagnosis of these two types of vasculitis and the clinical characteristics of WG with eosinophilia.

Case report

A 25-year-old woman was admitted to our department with fever, nasal congestion, ulcerated palpable purpurae in her upper and lower extremities, and suprascleritis. She did not have cough, sputum, or dyspnea. Two years before admission, she had arthritis of the bilateral knees and ankles, which was diagnosed as rheumatoid arthritis (RA). She was prescribed auranofin but it failed to improve her arthritis. One and a half years before admission, she had hemoptysis and chest roentgenography revealed the abnormal shadows of the bilateral lungs. Drug-induced pneumonia was suspected. After stopping the intake of auranofin, hemoptysis and lung abnormal shadows disappeared. Eight months before admission, nasal congestion and skin purpurae in both the lower extremities developed and persisted. Three weeks be-

From the Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, Tokyo

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Reprint requests should be addressed to Dr. Hirofumi Shoda, the Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655

Figure 1. Cranial magnetic resonance imaging enhanced with gadolinium. T1-weighted imaging. The mucosa of nose and right paranasal sinus became thick.

fore admission, low-grade fever developed and her family doctor diagnosed the suprascleritis of the left eye. She had a history of allergic rhinitis in her childhood, but had no history of asthma. The numbers of eosinophils in the peripheral blood were not examined before admission to our hospital.

She was hospitalized and administered a prednisolone therapy of 20 mg per day before the definite diagnosis of the disease to prevent the sclera perforation. Her laboratory data just before the corticosteroid administration showed increased numbers of white blood cells (WBCs), eosinophils, and platelets in her peripheral blood (WBC, 9,800/ μ l; eosinophil, 32.5%, 3,185/ μ l; and platelets, 54.8×10^4 / μ l). Normocytic anemia was present (hemoglobin, 8.8 g/dl). Liver and renal functions were normal and urinary sediment did not include occult blood, casts, or an abnormal level of protein. Systemic inflammatory responses were present (CRP, 4.88 mg/dl; ESR, 93 mm/h). She was positive for rheumatoid factor (RF) (RF 448 IU/ml) and negative for an anti-nuclear antibody. PR3-ANCA was present at a high titer (PR3-ANCA, 246 EU), but MPO-ANCA was absent. Immunoglobulin E (IgE) level was elevated (IgE, 2,100 IU/ml) and a radioimmunoassay test revealed the existence of the IgE specific for house dust. The level of immune complex was less than the detection level. The X-ray examination of her knees and ankles showed no erosive change. Computed tomography of her chest revealed diffuse ground-glass opacities in the bilateral lungs. Head MRI detected increased mucosal thickness of the nasal and right paranasal

Figure 2. Biopsy sample of nasal mucosa. Granulomatous inflammation contains giant cells, neutrophils, lymphocytes and eosinophils (arrowhead) (HE stain, $\times 200$).

Figure 3. Transbronchial lung biopsy sample. Eosinophilic infiltration of alveolar septums (HE stain, $\times 200$)

sinus (Fig. 1). A biopsy of the nasal mucosa was performed, which showed granulomatous inflammation and infiltration of lymphocytes, neutrophils, and eosinophils (Fig. 2). Skin biopsy showed the vasculitis of small vessels in the deep dermis. Bronchial fibroscopy was performed and because bronchoalveolar lavage fluid (BALF) was bloody and included macrophages with hemosiderin, pulmonary hemorrhage was diagnosed. BALF also included more than 30% of eosinophils. The specimen of transbronchial lung biopsy (TBLB) showed the infiltration of eosinophils in the alveolar septum (Fig. 3).

We diagnosed WG on the basis of ACR criteria and

Table 1. Wegener's Granulomatosis with Peripheral Eosinophilia

	Age/Sex	Involved Organs	Eosinophil count in the blood (/μl)	ANCA	Treatment
Potter (1999)	29/M	N, S, J, L (AH)	2805	c-ANCA	PSL, MTX, ST
	39/F	N, S, J, L (AH)	4484	c-ANCA	PSL, MTX, ST
Lane (2001)	nd	L, K	7000	PR3-ANCA	nd
Kamali (2003)	21/F	N, S, J, L (AH), K	2440	PR3-ANCA	mPSL, IVCY, PP
Our patient	25/F	N, E, S, J, L (AH)	3185	PR3-ANCA	PSL, MTX, IVCY

M: male, F: female, N: nose, E: eye, S: skin, J: joint, L: lung, AH: alveolar hemorrhage, K: kidney, c-ANCA: cytoplasmic antineutrophil cytoplasmic antibody, PR3: proteinase 3, PSL: prednisolone, mPSL: methylprednisolone, MTX: methotrexate, ST: sulfamethoxazole/trimethoprim, IVCY: intravenous cyclophosphamide, PP: plasmapheresis, nd: no data.

increased the dose of prednisolone to 50 mg per day. Because her left sclera thinned markedly, the transplantation of sclera was also performed. In addition to these therapies, a low-dose pulsed methotrexate (MTX) (15 mg weekly) was administered orally. Soon after these therapies were introduced, the number of eosinophils in the blood decreased less than 500/μl, the serum CRP level became within the normal range, and the serum level of PR3-ANCA began to decrease. Her nasal congestion and skin purpurae improved and abnormal chest radiographical shadow vanished. However, the suprascleritis persisted and we decided to treat her with intravenous pulsed cyclophosphamide (500 mg biweekly). After two courses of pulsed cyclophosphamide, her suprascleritis improved and serum level of PR3-ANCA became less than detectable level. No other causes of eosinophilia, such as parasites and drugs, were detected.

Discussion

The present patient developed granulomatous inflammation of the nasal mucosa, pulmonary hemorrhage, suprascleritis, and cutaneous vasculitis. She developed RF-positive arthritis, but we thought that her arthritis was due to WG rather than RA, because the X-ray examination showed no erosive change. She had a history of hemoptysis and abnormal chest radiographical findings one and a half years prior to admission. We could not rule out drug-induced pneumonia, but presumed the possibility that pulmonary hemorrhage due to WG remitted naturally at that time. PR3-ANCA was positive in this patient and we tentatively diagnosed her as WG on the basis of ACR criteria (1). However, eosinophilia was present in both the peripheral blood and tissue biopsy samples and the differential diagnosis of CSS was also considered. Sørensen et al proposed a diagnostic criterion for WG based upon the Chapel Hill consensus definitions (8). They proposed the absence of eosinophilia in both the peripheral blood and tissue samples as one of the criteria of WG. Our present patient did not fulfill this Sørensen's criterion for WG. Lane et al reported an evaluation of the Sørensen's diagnostic criterion and five patients with WG, which fulfilled the ACR criteria but not Sørensen's criterion

because of eosinophilia in both the peripheral blood and/or the tissue biopsy samples (6).

The present patient fulfilled three points of the ACR criteria for CSS, paranasal sinus abnormality, and eosinophilia in the blood and around the blood vessels in the biopsy samples (3). In addition, she showed an increased IgE level in the peripheral blood. However, she did not develop migratory pulmonary infiltration, or peripheral neuropathy, and she did not have a history of asthma. Rather, she had a history of allergic rhinitis. PR3-ANCA was present at a high titer in this patient. The percentage of WG patients with PR3-ANCA is much higher than that of CSS patients (2, 4). The present patient also developed granulomatous inflammation of the nasal mucosa, which is a rare finding in patients with CSS. For these reasons, we diagnosed this patient as having WG with eosinophilia rather than CSS.

Four cases of WG with peripheral eosinophilia (more than 1,500/μl) have been reported to date (Table 1) (5–7). According to the Hammanrich criteria for CSS, a peripheral blood eosinophil count of more than 1,500/μl is suggestive of CSS (9). However, the four previous cases and the present patient were considered as WG with eosinophilia in view of the involved organs and the existence of PR3-ANCA, even though their peripheral blood eosinophil count was higher than that level. Potter et al reported two cases of WG with eosinophilia in the blood, clinically characterized by a mild course, good prognosis, and good response to steroid therapy, and an absence of renal lesions (5). These two cases developed alveolar hemorrhage and remitted by the corticosteroid and MTX therapies. The clinical manifestation of our patient resembled these two cases, but our patient did not fully respond to MTX therapy. Kamali et al reported a poor prognosis of a case of WG with eosinophilia (7). We cannot determine which clinical course our patient will develop, and it is necessary to observe her clinical course carefully. We considered that it was necessary to treat her with sufficient doses of corticosteroid and immunosuppressive drugs in accordance with the standard therapy for WG.

Here, we reported a rare case of WG with eosinophilia in both the peripheral blood and the tissue biopsy samples and a high level of IgE.

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