Polyangiitis Overlap Syndrome with Eosinophilia Associated with an Elevated Serum Level of Major Basic Protein

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Polyangiitis overlap syndrome is a new disease entity and the reported cases in the literature are still limited. We describe a female patient presenting with finger ulcers, skin eruptions, pleural effusion, interstitial pneumonia and eosinophilia. Skin biopsy showed systemic small-sized angiitis and thrombosis. She was diagnosed as having polyangiitis overlap syndrome and was successfully then treated with corticosteroid. It is also of interest that the disease activity was correlated with the number of eosinophils in peripheral blood. The measurement of the serum level of major basic protein released from eosinophils functioning as a coagulant indicated the possible association of eosinophilia with thrombosis and polyangiitis.

(Key words: angiitis, eosinophilia, thrombosis)

Introduction

Leavitt and Fauci reported polyangiitis overlap syndrome in 1986 (1). It is defined as a systemic vasculitis that does not fit into a single disease entity of classical vasculitis, rather it overlaps several categories. As its concept is not well understood, the number of reported cases is still limited. The disease is characterized by manifestations of systemic vasculitis in the skin, lung, kidney, heart, gastro-entero system and peripheral nervous system, etc. and laboratory findings reveal acute phase reactants and leukocytosis with predominant eosinophils. We describe a patient diagnosed as having polyangiitis overlap syndrome with remarkable thrombosis in the extremities which seemed to be associated with eosinophilia.

Major basic protein (MBP) is one of the eosinophil granule proteins and its release during eosinophil degranulation can damage cells and tissues and work as a coagulant. This prompted us to measure the serum MBP level in the patient and it suggested the possible association of eosinophilia and the elevated concentration of MBP with the pathophysiology of the disease.

Case Report

A 66-year-old woman was admitted to our hospital on May 9, 1997 because of necrosis of the fingertip, intermittent claudication, and coldness and pain in the extremities. She had been treated as having Buerger’s disease since December 1996 and underwent surgery because of arterial obstructions in both the upper and lower extremities on angiography. At that time the white blood cell (WBC) was 8.1x10⁹/L (29% eosinophils) and C-reactive protein (CRP) was 1.52 mg/dl. Treatment included cilostazol (200 mg/day), ethylicosapentate (1,800 mg/day), diltiazem (100 mg/day), tocopherol nicotinate (300 mg/day), amitriptyline (30 mg/day), buprenorphine (0.6 mg/day) and alprostadil (10 µg/day). Necrotomy of her fingers was done in February 1997 and she was discharged in March (WBC 4.6x10⁷/L with 7.7% eosinophils). She visited our hospital on May 9, 1997 with the complaint of recurrence of coldness and pain in the extremities during the previous 2 weeks. She did not suffer from chest pain, dyspnea or anorexia. She had no prior vaccination, history of hepatitis, bronchial asthma, or any other allergic diseases. She had never smoked. Her family history was not contributory.

Her blood pressure was 134/82 mmHg in the right arm and 138/80 mmHg in the left arm, the pulse rate 70/min, regular, respiratory rate 16/min, and the body temperature was 36.2°C. She had no lymphadenopathy. There was no significant cardiac murmur and the breath sound was normal. Reduction of the ulnar pulses were observed in the presence of normal radial, foot and popliteal pulses. Abdomen and neurological examinations were unremarkable. Both hands were cold and necrosis was found on the 2nd and 3rd fingers of the right hand (Fig. 1). Thermographic image of the dorsum of the hand...
showed a reduction in the temperature of the fingers. She had small erythematous non-elevated eruptions on the bilateral lower extremities (Fig. 1).

Laboratory examinations on admission showed a red blood cell count of $4.41 \times 10^{12}/\text{l}$, leukocyte count $6.6 \times 10^{9}/\text{l}$ with 32.6% eosinophils ($2.16 \times 10^{9}/\text{l}$), and platelet count of $326 \times 10^{7}/\text{l}$. The liver function, renal function and electrolytes were all within the normal range. Erythrocyte sedimentation rate and CRP were slightly elevated (32 mm/h and 0.80 mg/dl, respectively). Serum immunoglobulin E (IgE) was 6 U/ml (normal, 40 to 300). Weakly positive test of anti-nuclear antibody ($80 \times$) was observed but specific antibodies including anti-DNA, anti-SS-A or anti-RNP antibodies could not be detected. Coagulation studies showed no abnormal sign. Anti-cardiolipin antibody and anti-neutrophil cytoplasmatic antibodies (cANCA and pANCA) were negative. The stool had normal flora and no parasite eggs.

Angiography of hands showed occlusions of small arteries such as bilateral ulnar arteries at the wrist joint, and most of the proper palmar digital arteries, and inadequate collateral circulation (Fig. 2). There was no obvious stenosis or occlusion in the proximal upper and lower extremities.

Left pleural effusion and interstitial changes in the left lower lung field were found on the chest X-ray and computed tomography (Fig. 3). Thoracentesis was carried out. Characteristics of pleural effusion; color: yellow, turbid; specific gravity: 1.035; leukocyte count: $10.7 \times 10^{9}/\text{l}$ with 72.0% eosinophils; total protein: 5.4 g/dl; albumin 2.5 g/dl; lactate dehydrogenase: 270 IU/l; glucose: 55 mg/dl; adenosine deaminase: 24.5 IU/l; culture: negative; cytology: class I) The histological finding of trans-bronchial lung biopsy showed interstitial pneumonia (Fig. 4). Thickening, fibrosis and infiltration of lymphocytes were shown in alveolar walls. Although the specimens did not contain vessels, they contained no eosinophilic invasion, evidence of malignancy, obvious epithelioid granuloma, caseous necrosis nor nodules. There was no detection of microorganisms. The punch biopsy specimen from a skin lesion of the right lower limb demonstrated mild angiitis with thrombosis (Fig. 5). The small arteries and arterioles had mild infiltrations of mononuclear cells and endothelial damage. However, no fibrinoid necrosis, eosinophilic invasion or granuloma was revealed. We diagnosed the disease as polyangiitis overlap syndrome.

Treatment with 50 mg/day prednisolone was started on May 24, 1997. Within two days, the pain in the extremities was resolved, and after 2 weeks, the lung and skin lesions were improved. The enlargement of necrosis was also stopped. On June 10, 1997, she was discharged from our hospital on 20 mg/day prednisolone with an eosinophil ratio of 1.0%. The patient has been in clinical remission without recurrent signs for 18 months.

We measured serum MBP at the points of both active and remission phase of the disease. Concentration of MBP in the serum was measured using BIACore™ from Pharmacia Biosensor AB (Uppsala, Sweden). Anti-MBP monoclonal antibody, 29-C-8, and standard purified human pro-MBP (2) were kindly provided by Dr. K. Yoshimatsu (Eisai Tsukuba Research Laboratory, Ibaraki). The concentration of serum level of MBP was determined based on a standard curve for a known concentration of purified pro-MBP. White blood cell and eosinophil count of her peripheral blood are also listed in Table 1. The MBP concentration on May 6, when the disease was most active, was 2,192 ng/ml. Subsequently it declined in parallel with the decrease in disease activity, and reached normal levels on July 3 as a result of the treatment.

**Discussion**

The disease of the present patient was characterized by mild...
angiitis accompanied by thrombosis in small-sized arteries and arterioles. She had systemic manifestations including lung, skin and extremities associated with eosinophilia.

In terms of the size of arteries affected, Buerger’s disease has occlusive disorders in small- and medium-sized arteries in the distal area of extremities and Takayasu’s disease involves larger-sized arteries or aorta. The size of affected arteries seen in our patient was smaller. Although small-sized arteritis is seen in polyarteritis nodosa, allergic angiitis and Wegener’s granulomatosis, the histological findings in the patient did not meet the criteria of these diseases because of the lack of fibrinoid necrosis, granuloma and infiltration of eosinophils. Henoch-Schönlein purpura is defined as a syndrome that can be characterized by many different types of small vessels vasculitis, but our patient was not young and did not show palpable purpura, abdominal pain, or nephritis. Hypersensitivity vasculitis is characterized by a vasculitic syndrome presumed to be associated with a hypersensitivity reaction following exposure to an antigen such as an infectious agent, a drug, or other foreign or endogenous substances. She did not have any drugs or antigenic stimulus prior to the onset of symptoms. Macropapular rash, palpable purpura and biopsy including arteriole showing granulocytes in a perivascular or extravascular location were not observed. Diagnosis of vasculitic syndrome associated with rheumatic syndrome was not made because our findings did not meet any definition of rheumatic diseases. Systemic angiitis in this patient was mild and thrombosis was seen in almost every small artery, which did not fit into any criteria of typical vasculitis and connective tissue diseases.

Leavitt and Fauci reported polyangiitis overlap syndrome in 1986 (1). It is defined as a type of systemic vasculitis that does not fit precisely into a single category of classical vasculitis but overlaps several categories. As its concept has not been widely accepted, the reported cases have been relatively rare (3–7). According to those descriptions, this disease is characterized by cutaneous lesions and systemic extracutaneous involvement such as lung, kidney, muscle, peripheral nervous system, gastro-entero-system, liver, and cardio-circulation system. The patients show elevated levels of acute phase reactants and leucocytosis, especially accompanied by eosinophilia. Diagnosis is done by ruling out other single diseases and is confirmed by biopsy.
Figure 3. Chest X-ray (A) and computed tomography (B) at time of admission showing left pleural effusion, interstitial pneumonia.

Figure 4. Histological findings of trans-bronchial lung biopsy showing interstitial pneumonia (HE stain, x100).

The present patient was diagnosed as having polyangiitis overlap syndrome, but the severity of the angiitis on the histopathological study was not very remarkable. It was noted that thrombosis in small-sized arteries was observed in almost every specimen. Angiitis accompanied by thrombosis produced the main features of the disorder. Studies of coagulation system presented no abnormality.

Although Leavitt and Fauci described that their patients were treated with corticosteroids and cyclophosphamide, there were reports showing patients with a prompt response to corticosteroids only. Our patient also responded well to treatment with prednisolone. Although the severity of angiitis or the affected tissues might be related to the response to corticosteroids, it will be necessary to investigate further accumulated cases with polyangitis overlap syndrome from the viewpoint of treatment.

In the present case, the most highlighted abnormality in the laboratory findings was eosinophilia: parasites, allergy, and collagen diseases were not associated with her disorders. The numbers of eosinophils were closely related to the activity of the disease. Because direct invasion of eosinophils was not observed in the tissues including lung and skin, we considered eosinophilia as one of the accelerating factors of her disorders. Eosinophils contain granules filled with cationic proteins (8) that are released upon activation and mediate eosinophil-induced tissue damage (9). MBP is the most abundant of the eosinophil granule proteins and its release during eosinophil degranulation can damage host cells and tissues. MBP has been reported to display many biological functions, including activation of basophils, neutrophils, mast cells and platelets. It also works as a coagulant in both arteries and veins in patients with eosinophilia. MBP inhibits the function of thrombomodulin through binding to the molecule resulting in the inhibition of protein-C activation (10) and hyper-concentration of MBP, therefore, causing hypercoagulation states (11). A high frequency of small vessel thrombosis in eosinophilia has been reported (12–15). It has also been described that the serum level of MBP is higher in patients with eosinophilia than in normal individuals.

We measured serum MBP levels in this patient using a real-time biospecific interaction analysis (BIA) based on optical detection by surface plasmon resonance. The MBP level in the
Figure 5. Histological findings of skin eruption biopsy showing mild angiitis with remarkable thrombosis (HE stain, A) ×100 and B) ×400).

<table>
<thead>
<tr>
<th>Date</th>
<th>May 6</th>
<th>July 3</th>
<th>Normal (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP (ng/ml)</td>
<td>2,192</td>
<td>928</td>
<td>904±348</td>
</tr>
<tr>
<td>WBC (×10⁹/l)</td>
<td>5.8</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Eo.</td>
<td>27.0%</td>
<td>1.0%</td>
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MBP: major basic protein, WBC: white blood cell, Eo.: eosinophil.

The patient was higher than that in the normal control. In addition, the MBP level was higher during the active phase with eosinophilia than that during remission period without eosinophilia. However, further study of the evaluation of the significance of MBP in the pathogenesis of the disease is necessary. MBP consists of pro- and mature-MBP, and mature-MBP is an efficient contributor to the prevention of thrombomodulin function. Mature-MBP accounts for a small fraction of total MBPs, and the level of mature MBP might not be completely correlated with the total MBP measured in this study. As the total MBP and mature-MBP may be released massively but transiently by degranulation of eosinophils upon activation, the detection of this transient elevation would be difficult. It will be necessary to accumulate cases and further investigate the correlation of the activity of polyangiitis in cases of eosinophilia with serum MBP.

References