Atypical Onset of Eosinophilic Granulomatosis with Polyangitis in a Patient with Long-term Well-controlled Bronchial Asthma

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Eosinophilic granulomatosis with polyangitis (EGPA) usually occurs in patients with a recent history (usually less than 10 years) of uncontrolled bronchial asthma. Here we describe a case of EGPA that occurred in a 68-year-old female who had well-controlled bronchial asthma for 17 years. A leukotriene receptor antagonist that had been prescribed one week before onset might have triggered the disease. Our case shows that there is a wide spectrum of clinical characteristics of EGPA, making diagnosis difficult in a primary care setting.

Keywords: bronchial asthma, eosinophilia, eosinophilic granulomatosis with polyangitis (EGPA), leukotriene receptor antagonist (LTRA) and poly-mononeuropathy

Introduction

Eosinophilic granulomatosis with polyangitis (EGPA), previously called Churg-Strauss syndrome, causes necrotizing vasculitis in small and medium-sized blood vessels.1 Among cases of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, EGPA is extremely rare (approximately one case per 1 million population per year) and its clinical characteristics in the Japanese population have not been well established. Clues for the diagnosis of EGPA are A) preceding bronchial asthma, B) eosinophilia and C) the presence of vasculitis. In general, about 80% of patients with EGPA have a recent history of moderate to severe asthma.2 However, Shimoi et al. reported that patients with a long history of asthma or even without such a past medical history can be diagnosed as having EGPA.3 This is a report of a case of EGPA showing an atypical manifestation and the clinical course.

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Case Presentation

A 68-year-old woman who had suffered from bronchial asthma for 17 years was admitted to our hospital following two weeks of prolonged fatigue, paralysis and dysesthesia of the extremities. Before admission, she had consulted her physician and was prescribed with montelukast. The paralysis was accompanied by pain and numbness which progressively spread from her right leg and further to the upper extremities. Her family history included Sjögren’s syndrome in her sister. She had no habit of alcohol or tobacco use. Medication included fluticasone inhalation, pravastatin and allopurinol.

On arrival, although she had an abnormal gait, she was afebrile and her vital signs were stable. Physical examination showed almost normal except for neurological findings. Results of manual muscle testing were as follows: 5/5 in bilateral biceps and triceps; 3/1 in right/left wrist flexors; 5/5 in bilateral wrist extensors; 5/5 in bilateral hip flexors; 5/3 in right/left hip extensors; 0/3 in right/left dorsal flexion and 1/3 in right/left ankle plantar flexion. The biceps, triceps and brachioradialis reflexes were bilaterally normal; however, right patella and bilateral achilles tendon reflexes were negative. Superficial perception was normal in the face and forearms, but it was decreased in the fingers of both hands and in the lower legs. Position and vibration senses were normal in the upper extremities but showed some disturbance in both of her lower legs.

The results of the laboratory tests were as follows: white blood cell count, 17,870/µL; eosinophilia (53.5%, 9,560/µL); erythrocyte sedimentation ratio, 59 mm/1 hour; rheumatoid factor, 49.5 IU/mL; myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA), more than 134 U/mL; C-reactive protein, 1.25 mg/dL; proteinuria and hematuria (Table 1). The results of electrocardiography and cardiac ultrasonography were normal. Pulmonary involvement was not detected by computed tomography, and the results of a respiratory function test were within the normal range. Though proteinuria and occult blood in urinalysis were seen on admission, renal biopsy was not seen as necessary.

A nerve conduction study showed that motor and sensory compound muscle action potentials of median, ulnar, tibial and peroneal nerves were bilaterally declined. Conduction of her left ulnar and median nerves was totally blocked between the left wrist and elbow, indicating poly-mononeuropathy. Hematoxylin and eosin staining of her left sural nerve showed an

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| RF: rheumatoid factor, ANA: antinuclear antibodies, PR3-ANCA: proteinase 3-anti-neutrophil cytoplasmic antibody, HPF: high power field.

Table 1. Laboratory data on admission.
invasion of eosinophils surrounding the nerve, while epithelioid granuloma was unapparent. Toluidine blue staining showed patchy deficits of myelinated nerve fibers, suggesting vasculitis.

Based on the diagnostic criteria published by the Japanese Ministry of Health, Labour and Welfare survey (1998), a definitive diagnosis of EGPA was made. As an initial treatment, 500 mg per day of methylprednisolone and cyclophosphamide hydrate was intravenously given for 3 days (Days 3 to 5). Subsequently, corticosteroid therapy was gradually tapered and a second course of cyclophosphamide hydrate was administered on day 31. The eosinophilia, abnormality in urinalysis and elevation of MPO-ANCA were improved by the treatment (Figure 1).

Her neurological symptoms, except for muscle strength of her left ankle dorsal flexion and the numbness of her left lower leg, disappeared within one month.

**Discussion**

The clinical course of our patient had some interesting points we should learn from. The first issue is the time interval from the initial episode of bronchial asthma and the occurrence of EGPA. As stated above, patients with EGPA characteristically have complications with moderate or severe asthma. Typically, asthma precedes the vasculitic phase by about 8 to 10 years. In the Japanese population, the average duration of precedent asthma was reported to be 6.1 years. Our case was unique in that EGPA occurred 17 years after the initial onset of asthma. Physicians should be aware that EGPA cannot be ruled out because of a long history of asthma.

The second issue is the relevance of severity of asthma and the occurrence of EGPA. In general, EGPA occurs in patients with a moderate or severe state of bronchial asthma. Respiratory symptoms in our patient were well controlled with an inhaled corticosteroid and there had been no asthma attacks for at least 5 years. We may need to recall EGPA as a possible differential diagnosis in patients with any state of bronchial asthma.

Since a first report on a relationship between administration of an LTRA and onset of EGPA, it has been a matter of debate. DuMouchel et al reported that there was a strong relevance between LTRA use and AGA. The possible pathophysiological mechanisms are assumed to be (i) allergic reaction to LTRA, (ii) leukotriene imbalance, (iii) altered cytokine pattern by LTRA, (iv) unmasking phenomenon due to alternatively tapered corticosteroid. Our patient was prescribed montelukast for one week which could be associated with the onset of EGPA. It was possible that...
the serum level of MPO-ANCA had already been elevated prior to the administration of LTRA; however, LTRA might have accelerated the onset of EGPA considering the clinical course. A previous study suggested that tapering or cessation of corticosteroid therapy directly triggered EGPA, while our patient had no history of systemic corticosteroid therapy before the onset. Further investigation is needed concerning this issue.

In the primary care setting, the recording of medical histories with great care is an essential tool for making a complete diagnosis. Our case was unique in terms of a very long interval (17 years) between the onsets of asthma and EGPA, in which EGPA occurred when asthma was well controlled. Due to its rarity, the clinical characteristics of patients with EGPA, especially in Japanese patients, have not been completely elucidated and a further accumulation of such cases is needed for a better understanding of the disease.

The authors state that there are no conflicts of interests to declare.

References