CASE REPORT

IgG and IgM Rheumatoid Factor Levels Parallel Interleukin-6 during the Vasculitic Phase in a Patient with Churg-Strauss Syndrome

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A 43-year-old woman with a 10-year history of bronchial asthma developed marked peripheral blood eosinophilia and symptoms of vasculitis. A diagnosis of Churg-Strauss syndrome (CSS) was made, and her symptoms were successfully treated with low-dose prednisolone. Serum rheumatoid factors (RF) of both IgG and IgM, but not IgA or IgE, subclasses transiently appeared in accordance with the vasculitic phase. Serum interleukin-6 (IL-6) levels also transiently increased in this phase, and the peak level was reached just prior to the maximum of RF elevation, suggesting the role of IL-6 as an inducer of RF. RF and IL-6 seemed to be involved in the pathogenesis of the vasculitis in this patient.

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Introduction

Churg-Strauss syndrome (CSS) is an uncommon disease of unknown etiology, characterized by eosinophilia, bronchial asthma, and symptoms due to angitis of multiple organs (1). Although the test for rheumatoid factor (RF) may be positive in about 50% of cases, its clinical significance and subclass involved in CSS are not known. On the other hand, interleukin-6 (IL-6) is a multifunctional cytokine produced by a variety of cells which has been suggested to play a role in diseases such as glomerulonephritis, multiple myeloma, and autoimmune diseases (2, 3). IL-6 can bind not only the cell surface α-IL-6 receptor but also the soluble IL-6 receptor (sIL-6R; soluble α chain), which can act as an agonist rather than an antagonist; i.e., the IL-6/sIL-6R complex can mediate IL-6 signals through interaction with the β chain (gp 130 chain) of the IL-6R complex (4). High levels of IL-6 lead to down-regulation of the α chain of IL-6R, resulting in unresponsiveness of the cells to IL-6. This refractory state could be overcome by the presence of sIL-6R (5). Thus sIL-6R may be an important factor controlling the IL-6 response in target tissues. Since IL-6-mediated signals are considered to be associated with polyclonal B cell activation and autoantibody production (2, 3, 6), it may be involved in the production of RF.

In this report, we describe a case of CSS with a transient vasculitic phase, and the results of serial measurements of serum IL-6, sIL-6R, and RF subclass.

Case Report

A 43-year-old woman with a family history of atopy developed bronchial asthma at the age of 33. Her asthma had been treated with inhaled becromethasone and β-stimulants, and also intermittent oral prednisolone on demand. She was otherwise well until November 27, 1992, when she suddenly noted general fatigue, systemic myalgia, and numbness of her hands and feet. On the other hand, she noted a gradual improvement of her asthma, as recorded by a peak-flow meter (Fig. 1). Such improvement in asthma is reported to coincide with the onset of the vasculitis (1).

The white-cell count was 12,400/mm³, with 44 percent eosinophils. Erythrocyte sedimentation rate and C-reactive protein (CRP) level were moderately elevated (34 mm/h and 3.2 mg/dl, respectively). Serial measurements of the eosinophil count and the CRP level are presented in Fig. 1. RF became positive and increased up to 720 IU/ml, then gradually decreased in accordance with the disease activity.

A non-steroidal anti-inflammatory drug (loxoprofen) was administered with some effect on her myalgias. She was then given 10 mg per day prednisolone for only 4 days and 10 mg...
RF Subclass and IL-6 in CSS

Figure 1. Correlation between symptoms and laboratory findings. Serial measurements of eosinophil count and CRP levels (upper panel), and peak expiratory flow rate (PEFR) (lower panel).

every other day for one month. Her symptoms were gradually improved. The test for RF became negative 18 weeks after the onset of symptoms due to vasculitis. Interestingly, her asthma gradually worsened and the peak-flow rates decreased following the disappearance of her myalgia.

With regard to RF subclass (determined by ELISA), IgG and IgM RF appeared in the vasculitis phase and disappeared following improvement of the symptoms. Neither the IgA nor the IgE subclass was detected throughout the clinical course, although the levels of serum total IgE were elevated in the vasculitis phase. The results of serial measurements of RF subclass, serum IL-6, and its soluble receptor are presented in Fig. 2. Serum levels of IL-6 were elevated when the symptoms of vasculitis appeared, and were followed by elevation of sIL-6R and IgG and IgM RF.

Discussion

The present patient, with a history of bronchial asthma, had a sudden-onset illness, manifested by myalgia, numbness of the hands and feet, an elevated erythrocyte sedimentation rate, leukocytosis with eosinophilia, and a positive test for RF. These symptoms and signs showed clinical features of CSS. This patient, however, was unusual because the vasculitis syndrome was easily brought into remission by small amounts of oral steroid. Obviously, inhaled steroid could not inhibit the onset of CSS, but may have contributed to the favorable course of this patient.

Of particular interest is the relationship between the symptoms due to vasculitis and RF. The appearance of RF was obviously connected with the vasculitis. We investigated class-specific RF, which has been studied in patients with rheumatoid arthritis (7, 8), and found that both IgG and IgM RF, but not IgA or IgE subclasses, were elevated in sera from this patient. High serum IgG RF levels are associated with the presence of extraarticular manifestations of RA, especially rheumatoid vasculitis (7, 8). IgG RF binds to IgM RF, which fixes complement, thus producing an immune-complex. Such an immune-complex is believed to cause vasculitis in RA. Furthermore, Aoki et al (9) described two patients of CSS with elevated levels of IgG RF in the vasculitic phase, as observed in our patient. These observations suggest that the levels of IgG and IgM RF might also be related to vasculitis in CSS.

Since IL-6 can augment the production of immunoglobulins, and is thought to induce autoantibody production (2, 3, 6), it is likely that IL-6 is involved in the production of RF. In accordance with this notion, we found that serum IL-6 was elevated quickly following vasculitic symptoms, and it increased to reach the maximum level prior to the peak serum RF levels. We also found that IL-6 seemed to induce sIL-6R production, as is
seen in the murine system (10), and sIL-6R levels were well correlated with RF. Excess production of both IL-6 and sIL-6R may contribute to the production of RF.

In conclusion, our observations suggest that IL-6 and RF played a permissive role in the pathogenesis of the vasculitis in this patient.

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References