Churg–Strauss syndrome associated with elevated levels of serum interleukin-5 and T cell receptor-Cβ gene rearrangement

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Abstract A 58-year-old woman was diagnosed with Churg–Strauss syndrome (CSS) based on the symptoms of bronchial asthma, eosinophilia, mononeuritis multiplex and histological examination of the right sural nerve. Prior to treatment, the serum interleukin (IL)-5 level was high, and rearrangement of the T cell receptor (TCR) gene was identified. This is the first report of TCR gene rearrangement in a patient with CSS. The expanded T cell clone may be responsible for the overproduction of IL-5. Further studies are warranted to disclose a prevalence of TCR gene rearrangement in CSS patients and its pathophysiological roles in the development of this disease.

Keywords Churg–Strauss syndrome · T cell receptor · Gene rearrangement · Interleukin-5

Introduction

Churg–Strauss syndrome (CSS), also known as allergic granulomatous angitis, is a systemic vasculitis syndrome characterized by bronchial asthma, allergic rhinitis, eosinophilia and granulation tissue with eosinophil infiltration. During the Chapel Hill International Consensus Conference in 1994, CSS was defined as a necrotizing vasculitis affecting small- to medium-sized vessels with eosinophil-rich and granulomatous inflammation [1]. However, the etiology of CSS has not been fully elucidated. Based on the determination of anti-neutrophil cytoplasmic antibodies (ANCA) in serum samples from patients with CSS, CSS has been considered to be an ANCA-associated systemic vasculitis. However, the association between ANCA and the clinical features of CSS has not been clarified.

Interleukin (IL)-5 is a T helper 2 cytokine known as a mediator in eosinophil activation, which has been thought to be involved in the etiology of CSS. T cell receptor (TCR) gene rearrangement, which usually induces lymphoproliferative disorders, can induce monoclonal T cell proliferation and also the overproduction of a specific cytokine. It has therefore been speculated that TCR gene rearrangements may play an important role in the pathogenesis of CSS. To the best of our knowledge, there are currently no reports of CSS linked to TCR-Cβ gene rearrangement.

Case report

A 58-year-old female developed bilateral leg weakness and severe pain in early July 2009. One month earlier, she had been diagnosed with bronchial asthma based on the presence of expiratory wheezing. Her symptoms of bronchial asthma had been relieved by inhalation therapy with salmeterol and budesonide. There was no family history of any connective tissue diseases. She visited a neighboring hospital, and laboratory examination showed marked eosinophilia, suggesting eosinophilic leukemia. Southern blot analysis for TCR gene rearrangement revealed rearranged bands of the TCR-Cβ gene (Fig. 1). In early August, the patient’s leg pain worsened, and she was referred to our hospital for further examination and treatment.
A physical examination on admission showed paralysis and sensory disturbance in the bilateral lower extremities, which were compatible with a diagnosis of mononeuritis multiplex. Petechiae were not apparent. Neck lymph nodes were not palpable. Her blood pressure was 161/88 mmHg, heart rate was 85 beats per minute and body temperature was 36.3°C. The results of laboratory tests on admission were: white blood cell count, 20,600/μl (neutrophils 20.8%, lymphocytes 12.9%, monocytes 2.3%, eosinophils 63.9%, basophils 0.1%); hemoglobin, 14.2 g/dl; platelet count, 335,000/μl; C-reactive protein, 0.98 mg/dl; erythrocyte sedimentation rate, 35 mm/h; blood urea nitrogen, 13 mg/dl; serum creatinine, 0.5 mg/dl; Na, 137 mEq/l; K, 5.0 mEq/l; Cl, 102 mEq/l; serum immunoglobulin E, 2,982 U/ml. The serum IL-5 level was 72.2 pg/ml. Tests were positive for rheumatoid factor (43 U/ml). There was no positivity for myeloperoxidase-ANCA (MPO-ANCA) nor proteinase 3-ANCA. Urinary protein excretion was 0.04 g/day. A fecal occult blood test was positive, and colonoscopy revealed colitis with erosion and several adenoma polyps. The cerebrospinal fluid had a normal cell count and protein concentration. A chest X-ray did not reveal any abnormal findings. High-resolution computed tomography showed thickening of the bronchial wall in the lower lobes. Electrocardiography and echocardiography revealed no abnormalities. Abdominal ultrasound showed a cyst in the left kidney. Magnetic resonance imaging (MRI) of the head revealed nothing abnormal, and a lumbar MRI did not demonstrate any marked abnormalities. Histological analysis of a sural nerve biopsy specimen taken from the right leg revealed atrophic nerve tissue with the infiltration of eosinophils, plasma cells and lymphocytes. The diagnosis of CSS was established based on the presence of bronchial asthma, eosinophilia >10%, mononeuritis multiplex and extravascular eosinophils, meeting four of the six criteria for the classification of CSS developed by the American College of Rheumatology (ACR) in 1990 [2]. Steroid pulse therapy and cyclophosphamide pulse therapy were followed by the administration of 50 mg/day prednisolone (PSL). We initially administered 1,000 mg cyclophosphamide, but reduced the dose to 700 mg for the second to sixth days because of leukocytopenia and liver dysfunction. The patient’s neurological symptoms gradually improved thereafter, while eosinophilia and hyperimmunoglobulinemia E disappeared. The dose of PSL was gradually reduced without the patient suffering a relapse. The level of serum IL-5 normalized (<7.8 U/ml) during the course of treatment.

**Discussion**

Churg–Strauss syndrome is known as a systemic necrotizing vasculitis accompanied by bronchial asthma and eosinophilia. Findings from previous studies suggest that CSS is an autoimmune disease, and CSS is considered to be an ANCA-associated systemic vasculitis as well as Wegener’s granuloma and microscopic polyangiitis. Although triggers of ANCA production have not been fully clarified, it is known that ANCA-associated vasculitis is often worsened by infections. Therefore, one of the major causes of ANCA-associated vasculitis may be infections. Huugen et al. [3] reported that aggravation of MPO-ANCA is induced by bacterial lipopolysaccharide. However, ANCAs are reportedly present in <40% of patients with CSS [4, 5], and ANCAs are not included in the criteria for the classification of CSS developed by the ACR. Because a number of patients with CSS do not have ANCAs, such as the patient reported here, ANCAs may not be the primary cause of CSS.

IL-5 is an inflammatory cytokine secreted by T cells and mast cells that plays an important role in the activation of eosinophils. This cytokine has been studied to elucidate the association between its titer and the pathogenesis of allergic diseases with eosinophilia, such as bronchial asthma and allergic rhinitis. Thus, CSS, which presents with bronchial asthma and allergic rhinitis as preceding symptoms, has also been thought to be associated with IL-5. The disease activity of CSS has been found to be correlated with serum levels of IL-5 in several studies [6, 7].

It is known that TCR gene rearrangements are present in patients with hematological malignancies or viral infections. Monoclonal T cell expansion induced by TCR gene rearrangements can produce a specific cytokine and contribute to the pathogenesis of various inflammatory diseases. Based on their analysis of 60 patients with idiopathic persistent eosinophilia, Simon et al. [8] reported that clonal populations of abnormal T cells producing IL-5 were present in patients with this disorder, including eight
patients with clonal rearrangements of TCR. Matsunaga et al. [9] reported a case of T cell lymphoma with eosinophilia and high serum levels of IL-5. In this case TCRγ gene rearrangement in the cervical lymph node, identified by PCR analysis, was thought to be the cause of overproduction of IL-5 by lymphoma cells. However, to the best of our knowledge, there have been no reports of TCR-C\(\beta\) gene rearrangements identified in patients with CSS. Eight patients with abnormal T cell clones in Simon et al.’s study [8] met the diagnosis of hypereosinophilic syndrome (HES). CSS and HES share many clinical features, including neuropathy. In this regard, further studies are necessary to disclose whether clonal expansion of IL-5-producing T cells is commonly observed in CSS patients and whether it plays a pathophysiological role in the development of the disease.

Viral infections can also be the cause of monoclonal expansion of CD8\(^+\) T cells. However, it is rare for monoclonal T cell expansions induced by viral infections to be found in immunocompetent individuals; these are usually induced by cytomegalovirus and found in immunocompromised patients [10]. The mechanism which induced TCR-C\(\beta\) gene rearrangement in our patient could not be identified, but there were no malignancies found in the patient. Therefore, it is speculated that a viral infection induced the TCR-C\(\beta\) gene rearrangement, with elevated levels of IL-5 being involved in the development of CSS.

In summary, we have reported a patient with CSS complicated by elevated levels of serum IL-5 and TCR-C\(\beta\) gene rearrangement. The association between CSS and TCR gene rearrangement was not fully investigated. However, this case suggests that overproduction of IL-5, as a result of TCR gene rearrangement, may be involved in the pathogenesis and etiology of CSS.

Conflict of interest None.

References