

Case Report

Eosinophilia with organ involvement in 3 siblings

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summary

We describe 3 siblings who suffered from marked eosinophilia with organ involvement. One sibling, who experienced cervical lymphadenopathy and peripheral neuropathy with eosinophilia (5,834 cells/ μ L) following bronchial asthma, was diagnosed with Churg-Strauss syndrome (CSS) according to the criteria of the American College of Rheumatology. Another sibling, who suffered from severe asthma with persistent polyarthritis and eosinophilia (2,496 cells/ μ L), was also diagnosed with CSS according to the criteria of the Japanese Ministry of Health, Labour and Welfare. The remaining sibling, who had eosinophilic pleuritis with peripheral blood eosinophilia (699 cells/ μ L), did not fulfill the widely used criteria for CSS or hypereosinophilic syndrome (HES); however, he fit the newly proposed criteria for HES. Glucocorticoid treatment relieved their symptoms. Although the diagnoses and the criteria used for diagnosis differed between the siblings, all 3 patients showed common features such as eosinophilia with organ involvement that required treatment, indicating the possibility of familial eosinophilia (FE). Furthermore, the clinical features observed differed substantially from those of previously reported FE patients, therefore, these 3 siblings may be affected by a type of FE distinguishable from those previously described.

Key words—Churg-Strauss syndrome; hypereosinophilic syndrome; familial eosinophilia

Introduction

Eosinophilia may be caused by several factors, including allergic reactions, parasitic infections, and malignancy. Churg-Strauss syndrome (CSS) and hypereosinophilic syndrome (HES), which are rare disorders with an unknown etiology, are known to be accompanied by peripheral blood eosinophilia. However, they are clearly distinguished from allergic reactions because they have a distinctive feature, namely, organ damage^{1,2)}.

Many reports have described familial eosinophilia (FE) since the early 1900s^{3,4)}. In these families, the distribution of eosinophilia was suggested to involve autosomal dominant inheritance. Recently, another autosomal dominant type of FE has also been described^{5~7)}. The disorder was characterized not only by marked eosinophilia but also by progression to end-organ damage in some affected family members, similar to HES. Furthermore, some of these family members exhibited obstructive pulmonary diseases such as asthma.

We encountered 3 siblings who suffered from marked eosinophilia with organ involvement. One sibling fulfilled the criteria of the American College of Rheumatology (ACR) for CSS⁸⁾, whereas another did not fulfill the ACR criteria for CSS but did meet those of the Japanese Ministry of Health, Labour

and Welfare⁹⁾. The other sibling, who had pleuritis accompanied by eosinophil infiltration, did not fulfill the advocated criteria for CSS^{8~10)} or HES^{11,12)}. All 3 siblings required treatment with glucocorticoids (GC).

Although their diagnoses and the criteria used for diagnosis differed between the siblings, these 3 patients showed common features such as eosinophilia with organ involvement requiring treatment. Because CSS and HES are both uncommon disorders, we believe that these findings cannot be merely coincidental. Furthermore, the clinical features observed differed substantially from those of previously reported FE patients, therefore, these 3 siblings may be affected by a type of FE distinguishable from those previously described.

Case report

Case 1 : The sixth sibling (Fig. 1)

A 42-year-old female housekeeper acquired bronchial asthma in 2001. She was a non-smoker. In 2002, she noticed enlargement of the cervical lymph nodes and pruritus on her body. She then experienced paralysis of both her hands. Later, she was confined to her bed and was then admitted to our hospital. Physical examination showed severe distal upper limb weakness, paresthesia in the right upper and lower limbs, and eruptions on her trunk and ex-

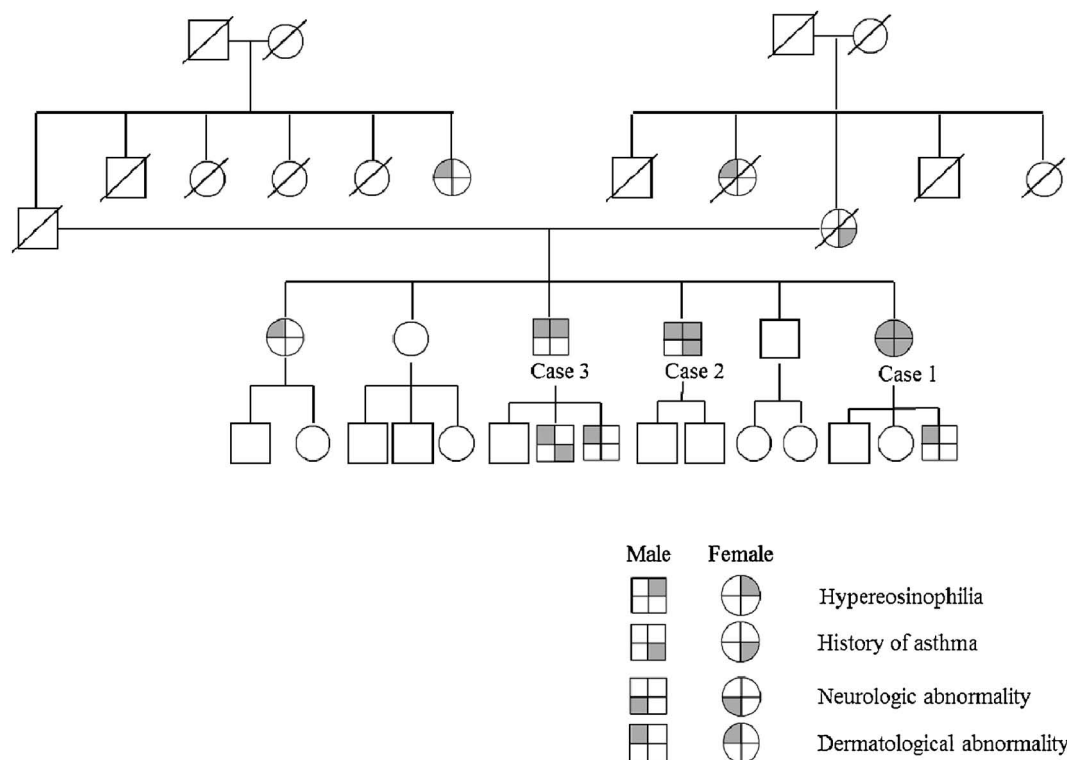


Figure 1. Family pedigree

Of 6 siblings, 3 had eosinophilia with organ involvement (Cases 1–3). The 3 siblings without eosinophilia did not have a history of asthma. Only the oldest sister had a skin disorder.

As for their parents, children, grandparents, and parents' siblings, 5 had dermatologic abnormalities and 2 had a history of asthma, but none had medical conditions similar to those seen in Cases 1–3.

tremities. Blood examination showed leukocytosis (13,260 cells/ μ L, 44% [5,834 cells/ μ L] of which were eosinophils). The C-reactive protein (CRP) level was slightly elevated (1.49 mg/dL). Serum IgE level was elevated (625 IU/mL); however, IgE specific to multiple inhaled or ingested allergens was not detected by the CAP-RAST method. Myeloperoxidase and proteinase-3 antineutrophil cytoplasmic antibodies (MPO-ANCA and PR3-ANCA, respectively) were negative. A nerve conduction study showed a mononeuropathy multiplex pattern. Neuromuscular and skin biopsy showed severe microvasculitis around the peripheral nerves with eosinophil infiltration. The bone marrow aspirate showed a slightly elevated eosinophil count (10%); however, no atypical cells were seen. The cause of eosinophilia could not be ascertained even after considering medication as a potential cause. She was diagnosed with CSS in accordance with the ACR criteria⁸⁾. After treatment with 40 mg/day prednisolone, her peripheral blood eosinophil count decreased to 95 cells/ μ L, and she was able to walk again. Currently, she is being treated with 5 mg/day prednisolone, and her condition remains stable. Peripheral blood screening via

fluorescent in situ hybridization did not show a 4q12 deletion, indicating that the FIP1L1-platelet-derived growth factor receptor fusion gene was absent. Her IgE level returned to normal (98 IU/mL); however, a positive level (0.90 UA/mL) of a specific IgE against moths was detected, without any related symptoms.

Case 2: The fourth sibling (Fig. 1)

A 43-year-old male car manufacturer with a history of severe bronchial asthma since 1995 was admitted to hospital due to worsening asthma, a persistent high fever ($>38^{\circ}\text{C}$) for 2 weeks, and outbreak of rash on the extremities and back in 2004. He had smoked 1 pack of cigarettes daily for 22 years. Physical examination showed conjunctival injection, swelling with tenderness in the proximal interphalangeal and metacarpophalangeal joints, and papulae on the extremities and back (Fig. 2). Blood examination showed leukocytosis (11,400 cells/ μ L, 21.9% [2,496 cells/ μ L] of which were eosinophils). The CRP level was elevated to 13.60 mg/dL. Serum IgE level was normal (103 IU/mL). MPO-ANCA and PR3-ANCA were negative. Stool assay did not show the presence of parasites. Abdominal and pelvic computed tomography (CT) scan showed no enlarged lymph

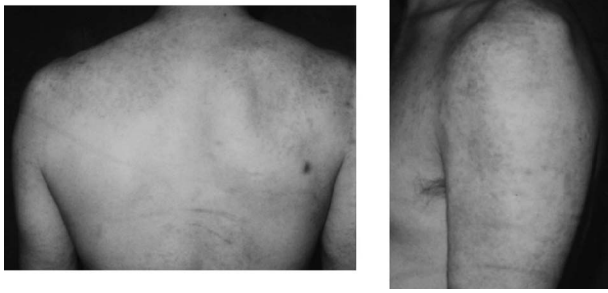


Figure 2. Skin findings in Case 2.
Papulae were seen on the extremities and back.

nodes or solid tumor. Upper gastrointestinal endoscopy showed no apparent abnormalities. Bone marrow aspirate showed normocellular bone marrow, with an elevated eosinophil count (20.5%) without atypical cells. No apparent etiology for eosinophilia, including allergic reactions, parasitic infections, or malignancy including malignant lymphoma, could be determined. Although his symptoms did not fulfill the ACR⁽⁸⁾ or Lanham's⁽¹⁰⁾ CSS criteria, he was diagnosed with CSS in accordance with the criteria of the Japanese Ministry of Health, Labour and Welfare⁽⁹⁾. He was treated with 30 mg/day prednisolone, which at once relieved his asthma, high fever, joint swelling, and rash. Two months later, he suffered from worsening of asthma with severe breathing difficulty; however, additional high-dose GC therapy relieved the dyspnea. He is currently being treated with 10 mg/day prednisolone and is experiencing no dyspnea or rash. Peripheral blood screening via fluorescent *in situ* hybridization did not show a 4q12 deletion. Serum IgE level was still normal (39 IU/mL) and no specific IgE was detected.

Case 3 : The third sibling (Fig. 1)

A 61-year-old male carpenter who did not have a history of asthma experienced repetitive prurigo all over his body and was being treated with intermittent low doses of GC since 2006. He had smoked 1 pack of cigarettes daily for 40 years. In 2005, before the appearance of the rash, his eosinophil count and serum IgE level were normal (288 cells/ μ L and 136 IU/mL, respectively). In 2009, during follow-up for prurigo, his eosinophil count was normal (341 cells/ μ L), however his serum IgE level was elevated (445 IU/mL) and specific IgE antibodies were detected: positive against bee venom (3.03 UA/mL) and borderline against cedar pollen (0.41 UA/mL), cypress pollen (0.39 UA/mL), rice (0.47 UA/mL), and wheat (0.42 UA/mL). In 2010, he noticed exacerbation of the rash and dyspnea on exertion, and CT scan detect-



Figure 3. Chest computed tomography findings of patient 3.
Chest CT showed right-sided pleural effusion.

ed a right pleural effusion (Fig. 3), following which he was admitted to our hospital. Physical examination showed prurigo on his trunk and extremities. Blood examination showed a normal leukocyte count of 6,030 cells/ μ L; however, the eosinophil count was slightly elevated (699 cells/ μ L). The CRP level was slightly elevated (1.42 mg/dL). Serum IgE level was also elevated (986 IU/mL). MPO-ANCA was negative; however, the PR3-ANCA level was slightly elevated (4.7 U/mL). The pleural effusion contained a number of leukocytes (3,567 cells/ μ L) and 60% of which were eosinophils. No atypical cells were found. Bone marrow aspirate showed normocellular bone marrow, with a slight elevation in eosinophils (7.1%) and no atypical cells. Peripheral blood screening using the fluorescent in-situ hybridization method did not show 4q12 deletion. No obvious cause of eosinophilia, other than occupation-related factors was noted. These features did not fulfill the World Health Organization classification for HES^(11,12); however, they did fulfill the recently proposed diagnostic criteria for HES by Simon et al.⁽¹³⁾. His symptoms were thought to be associated with eosinophilia because abundant eosinophils were seen in the pleural effusion and his eosinophil count was increasing even though he had stopped working. Therefore, we thought his eosinophilia with pleuritis might almost not be caused by occupation-related factors, and we decided to treat the patient with GC to prevent his condition from deteriorating. The presence of eosinophils in the peripheral blood and pleural effusion were improved immediately after initiating treatment with 35 mg/day prednisolone. Dyspnea and prurigo also improved in the following weeks; GC was tapered and then stopped in 2011. Four months after cessation of GC, the serum IgE level returned to normal (157 IU/

mL) ; however, the level of IgE specific to bee venom was borderline (0.63 UA/mL).

Additional family studies (Fig. 1)

These 3 patients had 3 other living siblings. Both parents had already died. Their mother had a history of asthma ; however, she had not had any skin diseases or neuropathy. Among their siblings, only the oldest sister had a skin disorder.

Discussion

It is quite rare that more than 1 case of CSS or HES were seen in the same family. The annual incidence of CSS and HES is reportedly 1.2–1.8 and 0.35 per 1 million people, respectively^{14~16)}. However, the incidence of CSS and HES is very high in the present family, because 2 cases of CSS and 1 case of HES are seen among 6 siblings. Therefore, this family may represent a unique pedigree.

It is true that CSS and HES are rare disorders ; however, secondary eosinophilia is not. Thus, it is important to exclude secondary causes of eosinophilia. We carefully examined potential underlying causes of eosinophilia in our 3 patients, including travel history, medication, and parasitic infection. However, excepting case 3, no apparent cause of eosinophilia was found. Moreover, as the occupation of the 3 siblings differed and they had lived separately for decades until the disease occurred, it is unlikely that they were exposed to common environmental factors that induced the eosinophilia. Table 1 summarizes IgE levels and specific IgE results for 3 patients. It is difficult to deny the allergic diathesis with subclinical level in case 1. Regarding the data and clinical history in case 3, it may be that the patient is susceptible to allergies and was exposed to an antigen associated with his occupa-

tion. However, his eosinophil count was normal until pleural effusion occurred, and his symptoms deteriorated despite his avoidance of antigens. Thus, his eosinophilia leading to organ involvement may have been caused by factors unrelated to his occupation. Moreover, serum IgE levels and specific IgE results differed in each case, suggesting that eosinophilia with organ involvement in our 3 cases may have been caused by nonallergic factors independent of IgE-mediated mechanism. We therefore suggest that the eosinophilia in our patients may not be a secondary cause.

Familial occurrence of persistent eosinophilia is called FE. FE was first documented in 1909³⁾. In 1964, Naiman⁴⁾ reported a 3-generation family with 7 affected patients, as well as 17 published families overall. In this report of FE, the term “hereditary eosinophilia” was used, which was defined as the presence of significant eosinophilia (>400 cells/ μ L), familial incidence, and the absence of other recognized causal factors. Although there are no established criteria for FE, we may be able to regard our 3 patients as having FE according to Naiman’s definition.

Recently, Lin⁵⁾, Rioux⁶⁾ and Klion⁷⁾ investigated 5 generations of a same family with marked eosinophilia. They described that FE was an autosomal dominant disorder and that some of the affected members showed organ involvement similar to that seen in HES. In their report, the authors compared family members with eosinophilia to those without eosinophilia. They reported that no clinical abnormality was more frequent in members with eosinophilia, although asthma was significantly more common in those family members without eo-

Table 1. Serum IgE levels and result of specific IgE in 3 cases

Case No.	Before Onset	Before Treatment	After Treatment
Case 1			
IgE (IU/ml)	NA	625 ^b	98
Specific IgE ^a	NA	Negative ^b	Positive against moth
Case 2			
IgE (IU/ml)	NA	103 ^b	39
Specific IgE ^a	NA	NA	Negative
Case 3			
IgE (IU/ml)	136	986 ^b	157
Specific IgE ^a	NA	Positive against bee venom and borderline against cedar pollen, cypress pollen, rice, and wheat ^c	Borderline against bee venom

Abbreviations: IgE, immunoglobulin E; NA, not available.

^a Specific IgE against multiple inhaled or ingested allergen was tested by CAP-RAST method.

^b Just before treatment

^c One-year before treatment

sinophilia, and immunologic analysis in affected members showed a relative lack of eosinophil activation compared to that seen in non-familial HES. Therefore, they concluded that their FE could be distinguished from non-familial HES⁷⁾. This study also showed that the eosinophil count in relatives without eosinophilia did not increase at any time-point; hence, long-term follow-up was not necessary for unaffected family members⁵⁾. Our patients, however, appear to differ from those previously reported, as 2 of the 3 affected siblings (Cases 1 and 2) had asthma, in addition to the eosinophilia and associated symptoms. Furthermore, patient 3 had a normal eosinophil count in 2005, when he exhibited no symptoms; however, his eosinophil count increased in 2010. These findings indicate that our patients differ from FE described by Lin⁵⁾ and Klion⁷⁾.

We may be able to regard our patients as exhibiting another type of FE; however, evidence supporting our hypothesis is insufficient. First, our investigation of family history included only 4 generations of the family, which contained insufficient data because of an unsatisfactory health care system in the past. Moreover, a blood test for detecting eosinophilia was performed in only these 3 patients. A detailed family history of the next few generations and blood tests for detecting eosinophilia are needed. It may take several decades to investigate the occurrence of eosinophilia-related symptoms in the next generation. Second, genetic assessment, including for human leukocyte antigen (HLA), was not performed. Rioux⁶⁾ undertook a genome-wide linkage analysis to determine the molecular basis of FE. The results showed that a single locus of interest is found on chromosome 5q31–q33, which contains the genes for interleukin (IL)–3, IL–5, and granulocyte-macrophage colony stimulating factor. However, no functional polymorphism was found. Tsurukisawa¹⁷⁾ also reported familial CSS in 2 sisters and performed HLA typing of family members; however, no difference was found in the frequency of different HLAs. These findings indicate that the genetic basis of FE may be complicated. Third, the age of onset was relatively high in our patients. In the reports of Lin⁵⁾ and Klion⁷⁾, eosinophilia was documented as early as 4 months of age. However, many family members developed organ involvement at the age of 50 years and older. Therefore, secondary events may be responsible for disease progression in addition to the eosinophilia itself, as they discussed⁷⁾.

In conclusion, we describe 3 siblings with eo-

sinophilia and organ involvement. We believe that the occurrence of these 3 eosinophilia cases in a single family is not a coincidence and that these patients may be exhibiting a type of FE different from those previously reported. Further studies are needed to clarify these findings.

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