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作成者（著者）	Chiaki, Arai / Kota, Wada / Sawako, Yanagisawa / Kentaro, Matsuura / Toshinari, Suetsugu / Hideo, Edamatsu
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Case Report

Hypereosinophilic Syndrome after Surgery for Eosinophilic Chronic Rhinosinusitis: A Case Report

Chiaki Arai Kota Wada* Sawako Yanagisawa
Kentaro Matsuura Toshinari Suetsugu and Hideo Edamatsu

Department of Otolaryngology (Omori), School of Medicine, Faculty of Medicine, Toho University

ABSTRACT: Hypereosinophilic syndrome (HES) is a rare disease in which eosinophilia causes organ damage and dysfunction. We describe a case of HES that developed during follow-up for eosinophilic rhinosinusitis. A 61-year-old woman presented with rhinorrhea, nasal obstruction, sneezing, snoring, and aural fullness. Endoscopic endonasal surgery, inferior turbinectomy, and septoplasty were performed for eosinophilic chronic rhinosinusitis, allergic rhinitis, and deviated nasal septum during the year she first visited our hospital. Nine months after surgery, she presented with a fever (37.2–38℃) of 2 weeks' duration, bilateral numbness of the lower leg, and lassitude. On the basis of her clinical course, we were able to differentiate her condition from eosinophilic granulomatosis with polyangiitis (EGPA), and HES was diagnosed based on high eosinophil counts and bone marrow puncture results. While treating eosinophilic chronic rhinosinusitis, otorhinolaryngologists must evaluate both the general condition of the patient and affected sites and consider the possibility that a systemic disorder such as EGPA or HES may develop during the clinical course.

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KEYWORDS: eosinophilia, hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), Churg-Strauss syndrome, eosinophilic chronic rhinosinusitis (ECRS)

Hypereosinophilic syndrome (HES) is a rare disease in which organ damage and dysfunction are caused by eosinophilia.[1–3] Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome), which likewise involves eosinophilia, has many of the clinical features of HES; differentiating between these entities is thus important.[4] The disease entity eosinophilic chronic rhinosinusitis (ECRS) — which is characterized by pronounced eosinophil infiltration of the parasinus mucosa and nasal polyps — has recently been proposed in Japan.[5] ECRS is similar to chronic rhinosinusitis with nasal polyp (CRSwNP), as defined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2012.[6] We recently assessed and treated a patient who developed HES during treatment after endoscopic sinus surgery (ESS) for ECRS. EGPA was suspected based on her clinical course, but the condition was ultimately diagnosed as HES owing to eosinophilia observed in the bone marrow. Although otorhinolaryngologists commonly encounter and treat patients with ECRS, HES is quite rare. This report describes the present HES case and reviews some of the relevant literature.

Case Report

A 61-year-old woman with chief complaints of rhinorrhea, nasal obstruction, sneezing, snoring, and aural full-

6–11–1 Omorinishi, Ota, Tokyo 143–8541, Japan
*Corresponding Author: tel: +81–03–3762–4151
e-mail: wadakota@med.toho-u.ac.jp
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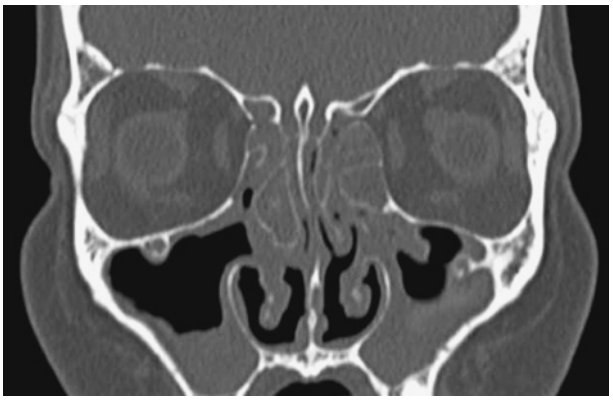

Fig. 1 Computed tomography (coronal view) scan of the paranasal sinus at the initial examination
The convex nasal septum is deflected to the left, and bilateral soft tissue densities are predominant over the ethmoid sinus.

ness during the previous week sought medical advice at the Department of Otolaryngology at Omori Medical Center, Toho University. She had received a diagnosis of bronchial asthma 2 years before her visit at our hospital and a diagnosis of sinobronchial syndrome 2 years after that diagnosis. She had been receiving the following therapy regimens: a budesonide/formoterol fumarate dihydrate inhaler (Symbicort®; AstraZeneca plc., London, UK), clarithromycin (Clarith®; Taisho Pharmaceutical Co., Ltd., Tokyo), and montelukast sodium (Singulair®; Merck & Co., Inc., Kenilworth, NJ, USA). She also had hypertension and allergic rhinitis. On the basis of intranasal findings, computed tomography (CT) findings (Fig. 1), and hematologic test results (eosinophil count: 2880/μl), we diagnosed her condition as ECRS, CRSwNP, allergic rhinitis, and deviated nasal septum. Endoscopic endonasal surgery, inferior turbinectomy, and septoplasty were performed under general anesthesia in the year she first visited our hospital. The excised bilateral nasal polyps showed conspicuous eosinophil infiltration but no evidence of vasculitis or granuloma. Thus, the surgical specimens were sufficient to render a diagnosis of ECRS. Postoperative treatment consisted of intranasal lavage with physiological saline and prescriptions for mometasone furoate hydrate (Nasonex®; Merck & Co., Inc.) nasal spray, clarithromycin, and montelukast sodium, along with oral betamethasone/dexchlorpheniramine maleate (Celestamine®; Takata Parmaceutical Co., Ltd., Tokyo), which was given for only 2 weeks postoperatively. Her postoperative course was favorable, with no intranasal exacerbations for a period of at least 2 years.

One year after surgery, the patient was examined at our department for a fever (37.2–38℃) of 2 weeks' duration, bilateral lower leg numbness, lassitude, and a 10-kg weight loss during the past 2 years. Intranasal findings were normal, with no evidence of sinusitis exacerbation (Fig. 2). Because her clinical course strongly suggested EGPA, montelukast sodium was immediately discontinued, and she was referred to the Department of Internal Medicine, where blood tests revealed eosinophilia (24624/μl) and elevated immunoglobulin E (IgE) (5550 IU/ml). The results were negative for proteinase 3 (PR3-), myeloperoxidase (MPO-), antineutrophil cytoplasmic antibodies (ANCA) and FIP1-like-1-platelet-derived growth factor receptor alpha (FIP1 L1-PDGFRA by fluorescence *in situ* hybridization). No appreciable organ damage was seen on chest radiography, chest-abdominal CT, echocardiography, abdominal echography, or gallium scintigraphy. There was no abnormality in a nerve conduction velocity study of the lower extremities. An iliac bone marrow examination showed marrow eosinophilia, as was the case with the nasal polyps, but no evidence of neoplastic changes (Fig. 3). Because our examination revealed no primary disease that could account for the eosinophilia, a diagnosis of HES was made on the basis of the negative test for FIP1 L1-PDGFRA, the results of the bone marrow pathology examination, the absence of vasculitis and granuloma on the pathologic findings, and the absence of organ damage. So she was determined not to be the state doubt actively EGPA. The patient was started on an immunosuppressant and corticosteroid regimen. She reports no numbness, and her clinical course has been uneventful (Fig. 4).

Discussion

The concept of idiopathic HES was proposed by Hardy and Anderson in 1968.[7] According to the World Health Organization (WHO) Classification of Tumors, released in 2001, HES is regarded as the same entity as chronic eosinophilic leukemia (CEL) and classified as a myeloproliferative disease.[8] The following three criteria are essential for an HES diagnosis: (1) increased peripheral blood eosinophil count ($\geq 1.5 \times 10^9$/l), (2) demonstrable eosinophilia in bone marrow, and (3) $<20\%$ myeloblasts in bone marrow and peripheral blood. Diagnostic exclusion criteria in the above classification are (1) all disorders that may involve secondary/reactive eosinophilia (*e.g.*, allergy, parasitic infestation, and vascular disorder due to collagen disease), (2)

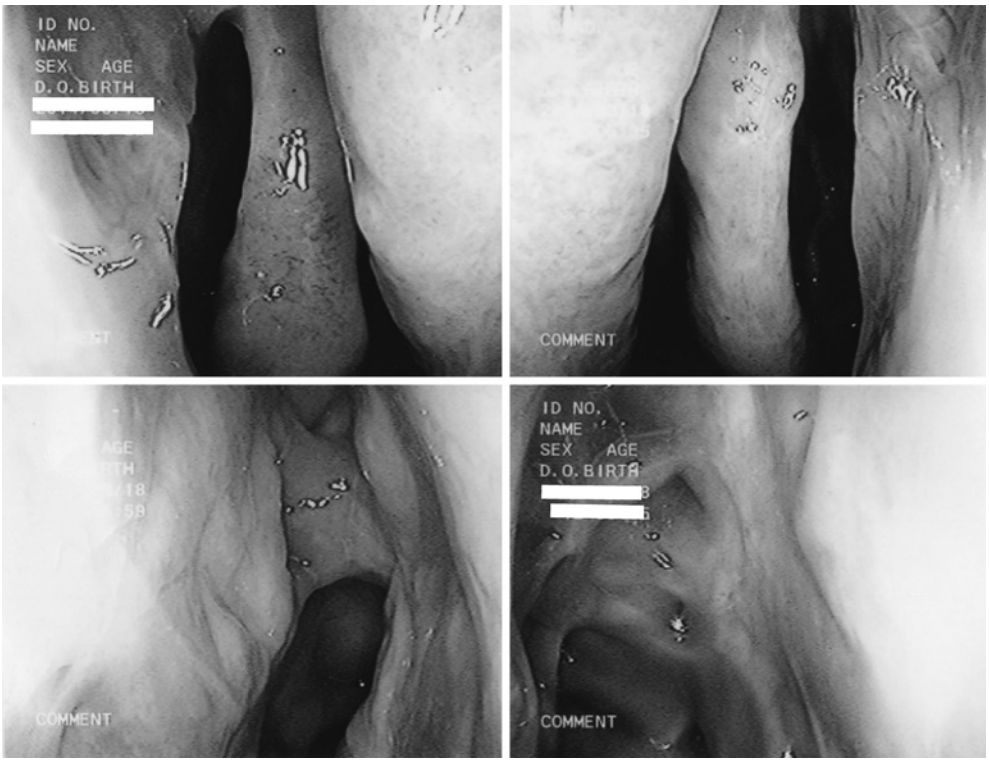

Fig. 2 Endonasal photograph
A photograph obtained when the patient's general condition had worsened. Both middle meatuses are widely dilated, while the ethmoid sinus mucous membrane is clean.

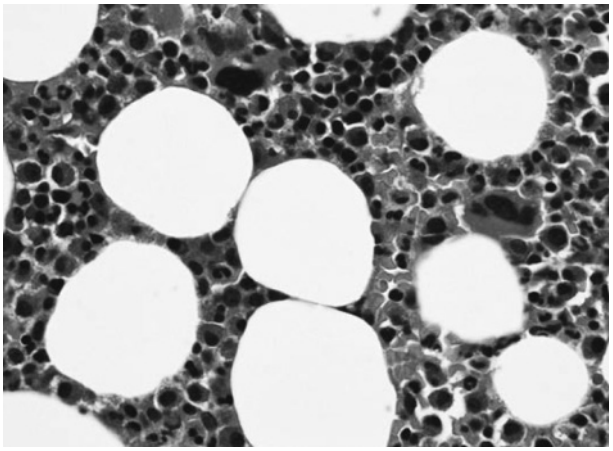

Fig. 3 Pathologic findings after iliac crest puncture
Eosinophilia is present in bone marrow (hematoxylin and eosin stain; magnification, 400×).

all malignant disorders that may involve secondary/reactive eosinophilia (*e.g.*, T-cell lymphoma, Hodgkin disease, and acute lymphoid leukemia), (3) eosinophil proliferation derived from tumor clones (*e.g.*, acute or chronic myelogenous leukemia), and (4) T-cell groups expressing aberrant surface characteristics or producing cytokines. The condition is diagnosed as CEL rather than HES when clonal eosinophilia that exhibits marrow cells with chromosomal aberrations or increased myeloblasts in peripheral blood or bone marrow is present in addition to the above findings. A specific gene abnormality, FIP1 L1-PDGFRA, was recently identified in some patients with HES. FIP1 L1-PDGFRA–positive HES is classified as CEL and categorized as a myeloid neoplasm associated with PDGFRA rearrangement, according to the 2008 WHO Classification of Tumors.[8] It has been reported that 14% of HES cases are FIP1 L1-PDGFRA–positive.[9,10] HES was diagnosed in the present case, in accordance with Gotlib's HES/CEL diagnostic and treatment algorithms,[11] *i.e.*, increased eosinophils in peripheral blood and bone marrow, absence of secondary/reactive eosinophilia, and a negative result on a test for the FIP1 L1-PDGFRA gene mutation. HES involves disorders of organs such as the heart, lung, brain, and liver, and HES patients may present with a wide variety of symptoms, such as fatigue, cough, dyspnea, angioedema, rash, fever, numbness, pain, and nasal symptoms.[12–14] Otorhinolaryngologists commonly encounter chronic rhinosinusitis in clinical settings, and an increasing number of ECRS patients have pronounced eosinophil infiltrates in nasal mucosa and polyps. A recent report noted

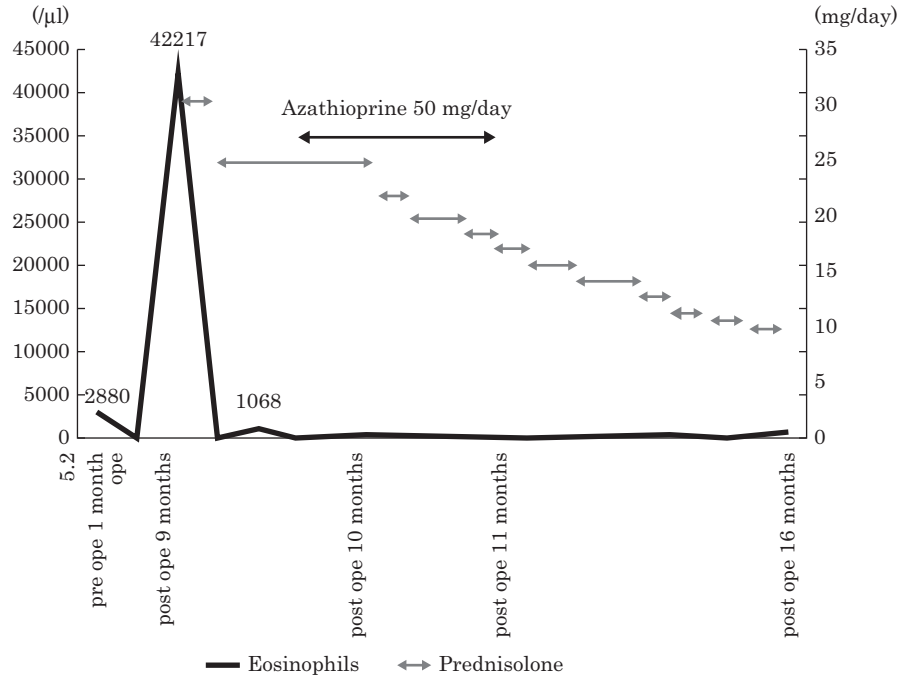

Fig. 4 Clinical course
The patient responded well to prednisolone therapy, exhibiting a rapid decrease in eosinophil count.
ope: operation

that ECRS accounts for 30% of chronic rhinosinusitis cases in Japan.[15] Our patient underwent surgery for ECRS, and her condition was later diagnosed as HES during follow-up. Because her peripheral blood eosinophil count was, remarkably, as high as 2880/μl before surgery, we cannot rule out the possibility that she had HES before surgery. No measures such as bone marrow puncture were taken because her symptoms were limited to the affected paranasal sinuses. These findings highlight the importance of considering the possibility of HES in ECRS patients with high eosinophil counts. The present case is the first to be reported in which HES developed during a course of treatment for ECRS and is therefore noteworthy.

HES treatment usually consists of corticosteroids and chemotherapeutic agents to control eosinophil proliferation and alleviate organ damage, but the condition is almost always refractory to such regimens and the prognosis thus grave. One report described a patient who favorably responded to imatinib, a tyrosine kinase inhibitor first clinically developed as a molecularly targeted therapeutic agent for cancer.[16] Imatinib was initially developed to target bcr/abl kinase, which is specifically expressed in Philadelphia chromosome-positive chronic myelogenous leukemia. Imatinib was later found to specifically inhibit c-kit and PDGFR kinase and was effective in treating FIP1L1-PDGFRA–positive HES.[17, 18] However, one study found that imatinib was effective in approximately 40% of cases of FIP1L1-PDGFRA–negative HES.[19] Gotlib's HES/CEL diagnostic and treatment algorithms are useful.[11] Further studies of treatments for FIP1L1-PDGFRA–negative HES are warranted. In the present case, treatment mainly comprised corticosteroids without the use of imatinib because the patient was FIP1L1-PDGFRA–negative. Fortunately, her clinical course has been favorable.

Until recently, the prognosis for HES has been poor, with a median survival period of 9 months and a 3-year survival rate of $<15\%$.[12, 20] This disappointing long-term survival is probably due to peripheral organ damage by eosinophils. However, one report found that 5-year survival rate has improved to $\leq 80\%$, owing to more effective adjunctive therapies, more active therapeutic approaches, and development of new treatment strategies.[11, 14]

Otorhinolaryngologists should understand that HES is sometimes fatal. In other words, systemic disorders such as HES or EGPA can arise during treatment for ECRS. Therefore, otorhinolaryngologists must evaluate both the affected sites and the patient's general condition. When any such disorder is suspected, immediate consultation

with a specialist may hasten diagnosis and treatment.

We described a case of HES that developed during treatment for eosinophilic sinusitis. It is important to be aware of the possibility that HES may lie dormant in patients with eosinophilic sinusitis. Early diagnosis is critical.

Summary

Hypereosinophilia developing during treatment for ECRS is extremely rare. Differential diagnosis of hypereosinophilia and EGPA is essential. Otorhinolaryngologists should be mindful of the possibility that hypereosinophilia and EGPA may be present in patients with ECRS.

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References

1) Cogan E, Roufosse F. Clinical management of the hypereosinophilic syndromes. Expert Rev Hematol. 2012; 5: 275-89.
2) Valent P, Gleich GJ, Reiter A, Roufosse F, Weller PF, Hellmann A, et al. Pathogenesis and classification of eosinophil disorders: a review of recent developments in the field. Expert Rev Hematol. 2012; 5: 157-76.
3) Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol. 2012; 130: 607-12.
4) Khoury P, Zagallo P, Talar-Williams C, Santos CS, Dinerman E, Holland NC, et al. Serum biomarkers are similar in Churg-Strauss syndrome and hypereosinophilic syndrome. Allergy. 2012; 67: 1149-56.
5) Ishitoya J, Sakuma Y, Tsukuda M. Eosinophilic chronic rhinosinusitis in Japan. Allergol Int. 2010; 59: 239-45.
6) Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl. 2012; 1-298.
7) Hardy WR, Anderson RE. The hypereosinophilic syndromes. Ann lntern Med. 1968; 68: 1220-9.
8) Bain BJ, Gilliland DG, Vardiman JW, Horny HP. Chronic eosinophilic leukaemia, not otherwise specified. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: WHO Press; 2008, p51-3.
9) Sada A, Katayama Y, Yamamoto K, Okuyama S, Nakata H, Shimada H, et al; Japanese Elderly Leukemia and Lymphoma Study Group. A multicenter analysis of the FIP1L1- αPDGFR fusion gene in Japanese idiopathic hypereosinophilic syndrome: an aberrant splicing skipping the αPDGFR exon 12. Ann Hematol. 2007; 86: 855-63.
10) Tanaka Y, Kurata M, Togami K, Fujita H, Watanabe N, Matsushita A, et al. Chronic eosinophilic leukemia with FIP1L1-PDGFR α fusion gene in a patient with a history of combination chemotherapy. Int J Hematol. 2006; 83: 152-5.
11) Gotlib J. World Health Organization-defined eosinophilic disorders: 2014 update on diagnosis, risk stratification, and management. Am J Hematol. 2014; 89: 325-37.
12) Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore). 1975; 54: 1-27.
13) Fathi AT, Dec GW Jr, Richter JM, Chen YB, Schwartzenberg SS, Holmvang G, et al. Case 7-2014: a 27-year-old man with diarrhea, fatigue, and eosinophilia. N Engl J Med. 2014; 370: 861-72.
14) Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol. 2009; 124: 1319-25.
15) Fujieda S, Sakashita M, Tokunaga T, Okano M, Haruna T, Yoshikawa M, et al. [Eosinophilic chronic rhinosinusitis]. Arerugi. 2015; 64: 38-45. Japanese.
16) Gleich GJ, Leiferman KM, Pardanani A, Tefferi A, Butterfield JH. Treatment of hypereosinophilic syndrome with imatinib mesilate. Lancet. 2002; 359: 1577-8.
17) Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med. 1996; 2: 561-6.
18) Holtz MS, Slovak ML, Zhang F, Sawyers CL, Forman SJ, Bhatia R. Imatinib mesylate (STI571) inhibits growth of primitive malignant progenitors in chronic myelogenous leukemia through reversal of abnormally increased proliferation. Blood. 2002; 99: 3792-800.
19) Müller AM, Martens UM, Hofmann SC, Bruckner-Tuderman L, Mertelsmann R, Lübbert M. Imatinib mesylate as a novel treatment option for hypereosinophilic syndrome: two case reports and a comprehensive review of the literature. Ann Hematol. 2006; 85: 1-16.
20) Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. The idiopathic hypereosinophilic syndrome: clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med. 1982; 97: 78-92.