Successful Treatment of Ulcerative Colitis Associated with Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia

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Abstract

A 23-year-old female was diagnosed as having simultaneous ulcerative colitis (UC) relapse and hypereosinophilic syndrome (HES)/chronic eosinophilic leukemia (CEL) without FIP1L1-platelet-derived growth factor receptor alpha (PDGFRA) (F/P) fusion gene. Pathological findings of colon specimens were compatible with UC, however, focal severe infiltration of eosinophils was observed in the rectum, which is unusual in UC, suggesting eosinophil-mediated organ damage. Although imatinib mesylate (IM) is usually ineffective for the treatment of HES/CEL with negative-F/P fusion gene, in the present case it led to the remission of HES/CEL and UC at a higher drug dosage level (400 mg/day). That suggested the presence of unknown tyrosine kinase abnormalities not yet categorized.

Key words: hypereosinophilic syndrome (HES), chronic eosinophilic leukemia (CEL), FIP1L1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFRA), ulcerative colitis, imatinib mesylate

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Introduction

When evaluating a patient with eosinophilia that is thought not to be secondary, differential diagnoses should be considered: 1) myeloid or lymphoid neoplasms associated with eosinophilia and platelet-derived growth factor receptor (PDGFR) or fibroblast growth factor receptor 1 (FGFR1) rearrangements, 2) clonal eosinophilia associated with an otherwise World Health Organization (WHO)-defined myeloid malignancy, 3) chronic eosinophilic leukemia-not otherwise specified (CEL-NOS), and 4) idiopathic eosinophilia (1-4). Hypereosinophilic syndrome (HES) is a subcategory of idiopathic eosinophilia, and the diagnosis requires the presence of a peripheral blood eosinophil count of 1.5×10⁹/L, or greater and eosinophil-mediated organ damage in the form of cardiomyopathy, pneumonitis, gastrointestinal inflammation, hepatosplenomegaly, and other manifestations (5). Based on the common feature of gastrointestinal inflammation, HES/CEL-associated organ damage might mimic inflammatory bowel disease (IBD), or act as a trigger of IBD relapse. The importance in correctly establishing the diagnosis of these molecularly characterized myeloid and lymphoid neoplasms can be emphasized because the PDGFRA/B fusion oncogenes are extremely sensitive to tyrosine kinase inhibitors such as imatinib mesylate (IM) (6-13). On the other hand, some FIP1L1-PDGFRA (F/P) negative HES/CEL has also been reported to respond to IM, usually at higher drug dosage levels (7, 14). Here we report a first case of the coexistence of HES/CEL and ulcerative colitis (UC), successfully treated with IM.

Case Report

A 23-year-old female was diagnosed with ulcerative colitis (UC), pancolitis type, and mesalazine was started in 2007. Before the treatment, the peripheral white blood cell (WBC) count was 6,000/µL. However, she discontinued tak-
ing mesalazine by self-judgement after remission. After half a year, UC relapsed with melena. In May 2009, she was referred to proctology department in our hospital. As the peripheral blood examination revealed a WBC count of 80,170/μL with 26% eosinophils, she was admitted to internal medicine. Physical examination on admission was unremarkable except for hepatosplenomegaly, palpable one fingerbreadth. Laboratory findings showed a WBC count of 53,830/μL, the differential 61% eosinophils (32,330/μL), 20% neutrophils and 6% lymphocytes, hemoglobin 13.1 g/dL and platelet count 33.2×10^4/μL. C-reactive protein was negative and liver and renal function was normal. The serum level of VitB12 was at the markedly high level beyond 1,500 pg/mL. IgE was 236 mg/dL and IL-5 was below 5.0 pg/mL, within normal range. The common causes of hypereosinophilia, including allergic, parasitic diseases were ruled out. The serum level of soluble interleukin-2 receptor was elevated to 5,940 U/mL. Abdominal computed tomography showed hepatosplenomegaly, however, no other lesion or lymph node swelling was found. An electrocardiogram was normal and transthoracic ultrasonic cardiology showed ejection fraction of 76%. Endoscopic findings of the colon showed continuous and diffuse mucus, erosions, ulcers and the disappearance of vascular patterns in total colon (Fig. 1A, B). Based on these findings, she was diagnosed with UC relapse of the moderate pancolitis type. Pathological findings of specimens obtained from colon biopsy revealed mucin depletion and severe chronic inflammation (Fig. 2A). Paneth cell metaplasia which is characteristic of IBD was also observed (Fig. 2B). Moreover, the crypt distortion and mucin depletion were observed in the sigmoid colon, compatible with IBD (Fig. 2C). Interestingly, focal severe infiltrations of eosinophils were observed in the rectum, which is unusual in IBD (Fig. 2D). The bone marrow aspiration and biopsy were performed. The bone marrow findings showed hyperplasia with an increase in all stages of eosinophilic differentiation up to 24.2%, less than 5% blasts (Fig. 3A, B). The karyotype was 46, XX, and chromosome 4q12 interstitial deletion (fluorescence in situ hybridization) was not detected. Based on these results, she was diagnosed with HES/CEL with negative F/P mutation. However, we cannot deny the possibility that F/P could be positive, because a molecular analysis of the F/P fusion mRNAs was not performed.

Mesalazine 1,500 mg/day and prednisolone (PSL) 40 mg/day was started, then PSL was increased to 50 mg/day. However, remission was not achieved, which is unusual in UC. Imatinib mesylate (IM) 100 mg/day was initiated and brought the recovery of diarrhea and melena. In July, she suffered from sepsis, which again caused an elevation of WBC and eosinophil count. Antibiotics were started with the increase of IM to 200 mg/day and addition of hydroxy-carbamide (HU) 500 mg/day. The WBC and eosinophil count was decreased and her general condition improved. However, UC relapsed with hypereosinophilia at the dosage of IM 200 mg/day, when HU was suspended. PSL and HU were re-started prior to IM, then the dosage of IM was gradually increased. Finally, IM at a dosage of 400 mg/day, resulted in the marked improvement of UC and hypereosinophilia, and enabled the discontinuance of PSL and HU. After that, remission of HES/CEL and UC was sustained (the WBC count about 4,000-5,000/μL and the differential of eosinophils 4-17%)(Fig. 4).

**Discussion**

Eosinophilia is caused by a variety of diseases, and categorized into allergic and parasitic diseases, and hematological disorders. In the relationship between UC and eosinophilia, rare cases of mesalazine-induced peripheral eosino-
philia have been reported (15-17). When mesalazine treatment was suspended, eosinophilia rapidly disappeared, confirming the direct responsibility of this drug. In the present case, mesalazine was started for the therapy of UC, then she discontinued taking the medicine by self-judgement after remission. After half a year, UC relapsed and marked eosinophilia was observed. Therefore, it seemed that mesalazine was not at fault in the cause of eosinophilia.

Concerning UC, colon-endoscopy showed colitis, and histology was compatible with UC, that is, crypt distortion and mucin depletion in the rectum. Interestingly, focal marked infiltration of eosinophils was observed in the rectum, which

Figure 2. A) Pathological findings of specimens obtained from the sigmoid colon revealed mucin depletion and severe chronic inflammation (Hematoxylin and Eosin staining, 100×). B) Paneth cell metaplasia which is characteristic of IBD was observed (arrow) (Hematoxylin and Eosin staining, 400×). C) Crypt distortion and mucin depletion was observed in the sigmoid colon, compatible with IBD (arrow) (Hematoxylin and Eosin staining, loupe). D) Focal severe infiltration of eosinophils was observed in the rectum, unusual in IBD (Hematoxylin and Eosin staining, 200×).

Figure 3. A) Bone marrow smear showed hypercellular marrow with an increase in all stages of eosinophilic differentiation up to 24.2% with less than 5% blasts (May-Giemsa, 1000×). B) Pathological findings of bone marrow revealed hyperplastic bone marrow with sheets of eosinophils (Hematoxylin and Eosin staining, 100×).
is unusual in UC. It might be eosinophil-mediated organ damage, because clonal eosinophilia and HES might be accompanied by eosinophil-mediated organ damage in the form of cardiomyopathy, pneumonitis, dermatitis, sinustis, central nervous system or peripheral neuropathy, gastrointestinal inflammation, hepatosplenomegaly, thromboembolic complications, and other manifestations.

Hematological disorders associated with hypereosinophilia can be classified as reactive, clonal or idiopathic. Reactive eosinophilias are associated with cytokine (IL-5) dependent phenotypically abnormal and/or clonal T lymphocytes. Clonal eosinophilia is distinguished from idiopathic eosinophilia by the presence of histologic, cytogenetic, or molecular evidence of an underlying myeloid malignancy. The 2008 WHO classification system for hematologic malignancies recognizes 2 distinct subcategories of clonal eosinophilia: CEL-NOS and myeloid/lymphoid neoplasms with eosinophilia and mutations involving PDGFRA/B or FGFR1 (2). CEL-NOS is defined by the presence of either a cytogenetic abnormality or greater than 2% peripheral blood blasts or greater than 5% bone marrow blasts (18). Cases that fail to meet any of these criteria are consistent with HES, if persistent eosinophilia (>1,500/μL) and the evidence of tissue damage are documented. The importance in correctly establishing the diagnosis of these molecularly characterized myeloid and lymphoid neoplasms with eosinophilia and mutations involving PDGFRA/B or FGFR1 is emphasized because the PDGFRα/B fusion oncogenes are extremely sensitive to tyrosine kinase inhibitors such as IM. In the present case, bone marrow smear and biopsy findings revealed hypercellular bone marrow with sheets of eosinophils without abnormal cytogenetics and F/P fusion gene. Although no abnormal T-cell population was identified, the possibility of secondary hypereosinophilia might be low, based on the serum IL-5 level of below 5.0 pg/mL.

In the management of HES, PSL is the cornerstone of therapy for HES. Either HU or interferon alfa is used as a PSL-sparing agent. IM is usually ineffective for the treatment of WHO-defined HES/CEL. However, occasional reports have described successful results with IM for F/P-negative patients, usually at higher drug dosage levels (400-800 mg/day), compared with the dosage of 100-400 mg/day in F/P-positive patients. In the present case, both mesalazine and PSL were started, however, remission was not achieved. Then, IM at the starting dosage of 100 mg/day was started, after informed consent was obtained. In accordance with the drastic effect for both eosinophilia and diarrhea, two possibilities might be considered: One is that IM suppressed the activating immune cells in UC and eosinophils in HES/CEL separately, and the other is that all her symptoms including bowel pathological findings might be due to HES/CEL, even though the pathological features of her colon were very typical for those in UC patients. Finally, IM led to the remission of HES/CEL and UC with the dosage of 400 mg/day, although not highly sensitive. That suggested the presence of unknown tyrosine kinase abnormalities not yet categorized.

Only one report of the coexistence of HES, autoimmune hepatitis (AIH), and UC has been reported (19). Although a
distinctly abnormal T-cell population could not be identified in the patient, the development of hypereosinophilia in the context of AIH and UC, two autoimmune conditions with a Th2 bias, was an argument for the lymphoid variant of HES. However, the more accurate term to describe eosinophilia associated with clonal or phenotypically abnormal lymphocytes is lymphocytic variant hypereosinophilia, not lymphocytic variant HES. Therefore, the present case is the first reported case to our knowledge, of the coexistence of HES/CEL and UC.

Although UC associated with HES/CEL is very rare, appropriate treatment of both HES/CEL and UC is important, because both deteriorate mutually and HES/CEL might act as a trigger of UC relapse.

The authors state that they have no Conflict of Interest (COI).

References


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