INTRODUCTION

Hypereosinophilia (HE) is generally a reactive condition, and therapy consists of treatment of the underlying disorders. Other causes of HE include myeloproliferative disorders, which induce HE primarily by preferential eosinophilic differentiation, and immunophenotypically aberrant T-cell subsets, which induce HE by overproduction of eosinophilopoietic cytokines. For HE caused by aberrant T-cell subsets, steroids are the cornerstone of the therapy, and cytotoxic and immunomodulatory agents are used for steroid-resistant patients. Malignant progression to T-cell lymphoma occasionally develops in cases caused by aberrant T-cell subsets. It is important, therefore, to pay close attention to the clinical course and modify treatment as required.

CASE PRESENTATION

A 53-year-old male visited our hospital complaining of dry cough, nasal congestion, painless systemic lymphadenopathies and skin rash. He had an anamnesis of emphysema and recurrent tonsillitis treated with tonsillectomy with no medication, and had no allergy.
sis. There was superficial lymph node swelling, and prurigo was observed on his face, trunk, and extremities. The blood examination presented HE and a high titer of immunoglobulin E (IgE) as measured by fluorescence enzyme immunoassay. There was no cytopenia in the peripheral blood and no blast cell proliferation in the bone marrow. The ova and parasite examination by stool and serum antibodies was negative. Cytogenetic tests analyzed by fluorescent in situ hybridization for Philadelphia chromosome and interstitial deletion on 4q12 resulting from the Fip1-like1 (FIP1L1) fusion gene and platelet-derived growth factor receptor alpha (PDGFRA) [1] were negative, and his karyotype was a normal 46 XY. We did not examine other types of molecular abnormalities associated with platelet-derived growth factor receptor beta (PDGFRB) or fibroblast growth factor receptor 1 (FGFR1). No aberrant T-cell subsets with CD3-CD4+ surface marker in the peripheral blood were present by flow cytometry. Analysis of other abnormal types was not performed. T-cell receptor (TCR) rear-

**TABLE 1.**

| Blood cell count          | Creatinine                | 0.71 mg/dL |
|---------------------------|---------------------------|------------|
| White blood cell          | Creatine phosphokinase    | 103 U/L    |
| Segented Neutrophil       | Sodium                    | 138.8 mmol/L|
| Monocyte                  | Potassium                 | 4.6 mmol/L |
| Eosinophil                | Chloride                  | 100.7 mmol/L|
| Basophil                  | Calcium                   | 9.1 mg/dL  |
| Atypical lymphocyte       | Vitamin B<sub>12</sub>     | 534 Pg/mL  |
| Lymphocyte                |                           |            |
| Red blood cell            | 445 x 10^4/μL             |            |
| Hemoglobin                |                           |            |
| Hematocrit                |                           |            |
| Platelet                  |                           |            |
| Biochemistry              |                           |            |
| Total protein             |                           |            |
| Albumin                   |                           |            |
| Total bilirubin           |                           |            |
| Alkaline phosphatase      |                           |            |
| Aspartate aminotransferase|                           |            |
| Alanine aminotransferase  |                           |            |
| Lactate dehydrogenase     |                           |            |
| γ-Glutamyltranspeptidase  |                           |            |
| Blood urea nitrogen       |                           |            |
| Elephant                  |                           |            |
| Human T-cell lymphotrophic virus I antibody | negative |

**Fig. 1.** Nodular lesions were distributed diffusely in both lung fields on the first chest CT.

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rangement was not detected in the peripheral blood by polymerase chain reaction (PCR) amplification for variable regions. Eosinophilopoietic cytokines such as interleukin-5 (IL-5) were not examined. The other laboratory data at the first examination is shown in Table 1. Normal ventricular wall motion and no valvular disorder were confirmed by echocardiography, there was no hepatosplenomegaly on abdominal computed tomography (CT), and there were diffuse patchy shad-

ows in both lung fields on chest CT (Figure 1). Follicular hyperplasia without atypical cells was present in histology from a swollen cervical lymph node, suggesting reactive lymphadenopathy and provided negative evidence for malignant lymphoma. HE continued for two months, and the patient was diagnosed as idiopathic hypereosinophilic syndrome (HES) based on the above data. Initial treatment consisted of prednisolone (PSL) of 40 mg/day. Early therapeutic response for PSL was good and dose tapering was begun. At the PSL dose of 2.5 mg/day, HE recurred and dose escalation was performed (Figure 2). After that, the patient complained of gingival ulcers, and pharyngoscopy revealed swelling of the root of the tongue (Figure 3). CT study confirmed the recurrence of cervical lymphadenopathies and a tumor-like lesion in the left upper lobe of his lung. Disease progression of HES was suspected and hydroxycarbamide (HU) was initiated with PSL 50 mg/day. The histological findings of the gingival specimen were prominent infiltration of eosinophils and lymphocytes, and atypical lymphocytes with CD4+ CD30+ surface marker (Figure 4), which did not present dysplasia sufficient to be diagnosed as malignant lymphoma. On the other hand, the histological findings of the root of the tongue showed the infiltration of eosinophils, lymphocytes and plasma cells without morphologically abnormal lymphocytes, and CD4+ CD30+ T-cells were also revealed in this

Fig. 2. Clinical course from the initiation of steroid monotherapy to the first recurrence.

Fig. 3. A swelling lesion around the root of the tongue was the first sign of exacerbation of HE.
sample. TCR gene rearrangement analyzed by southern blot was not detected from either sample.

One month after HU initiation, the patient experienced chest pain, and multiple nodular lesions were revealed by chest CT (Figure 5). Histology of those lesions demonstrated significant eosinophilic infiltration with necrotic change, therefore, we concluded that HU was not effective against HES and switched to cyclosporine (Cy) as the steroid-sparing agent. At first, the combination therapy of PSL and Cy was effective to some extent. However, as steroid dose was tapered, the blood eosinophil count began to increase and an acceptable maintenance steroid dose could not be obtained. Then, we changed Cy to interferon-α (IFN-α) in expectation of a greater steroid-sparing effect. Even with a subcutaneous IFN-α injection dose of three million international units every other day in combination with PSL dose from 10 to 20 mg/day, we could not keep the blood eosinophil count below 1500/μL. We concluded that IFN-α was not superior to Cy, and changed from IFN-α back to Cy again because of its cost and complicated injection procedure. Soon after switching to Cy, the patient complained of a choking sensation around his throat. Gastrointestinal endoscope test found elevating erosive lesions spread diffusely from the esophageal inlet to stomach (Figure 6a). The histopathological findings of these lesions showed prominent eosinophilic infiltration, similar to the earlier biopsy from his lung. Plain chest X-ray revealed aggravation of multiple nodular lesions in his lung fields, and abdominal CT presented mesenteric lymphadenopathies (Figure 6b). The eosinophil count, C-reactive protein (CRP) and soluble IL-2 receptor (sIL-2R) in the peripheral blood had elevated to 3975/μL, 8.86 mg/dL and 3020 U/mL, respectively. We diagnosed a major exacerbation of HES and increased the PSL dose again. The clinical course after disease exacerbation is shown in Figure 7. Considering the possible need for cytotoxic chemotherapy or bone marrow transplantation in the near future, we referred the patient to the hematological department of another hospital.

The patient approved the diagnostic procedures described in this report, and written informed consent was obtained.

**DISCUSSION**

There are three types of HE, reactive, that related to clonal disorders of the bone marrow, and HES. HES can be diagnosed after exclusion of the first two categories with persistent HE and damage to organs [2]. Among clonal disorders, myeloproliferative disorders associated with hypereosinophilia (M-HE) is caused by the specific proliferation of eosinophils against a background of clonal genetic abnormalities [3] generally related to tyrosine kinase, which plays an intracel-
lular signaling role in cellular proliferation [4]. The FIP1L1-PDGFRA (F/P) fusion gene is the most common cause of M-HE, and other abnormalities associated with PDGFRB or FGFR1 rearrangement are extremely rare [5]. Clinical and laboratory features associated with M-HE include hepatosplenomegaly, anemia, thrombocytopenia, bone marrow dysplasia or immaturity, elevated vitamin B12 level, and refractoriness to steroid therapy [6]. We did not examine all types of reported cytogenetic abnormalities except for chromosome 4q12, and there may be also unidentified abnormal genes related to M-HE [7], so we could not exclude the diagnosis of M-HE. Clonal disorders with reactive eosinophilia and other clonal disorders in which eosinophils are part of the neoplastic clone were excluded by the blood, bone marrow and biopsy sample analysis.

In HES patients, aberrant T-cell populations that secrete IL-5 had been reported [2], and the etiology of lymphocyte-variant hypereosinophilia (L-HE) is char-

Fig. 6. Elevating erosive lesions in the esophagus were revealed by gastrointestinal endoscopy (A), and abdominal CT presented mesenteric lymphadenopathies (arrow) (B).

Fig. 7. Clinical course after the first exacerbation of HE.
acterized by the presence of T-cell populations producing eosinophiloietic cytokines [7] defined by the phenotypically aberrant T-cell subsets and TCR gene rearrangement [8]. The clinical features of L-HE are lymphadenopathy, organ involvements of skin, lung and intestine, increased serum level of IgE, sIL-2R, and good response to steroid therapy [7]. Our case was considered to be idiopathic HES based on the diagnostic and treatment algorithm of the 2016 World Health Organization (WHO) classification of eosinophilic disorders [9], however, high serum IgE and sIL-2R levels, steroid response, and involved organs were suggestive of L-HE [10]. Negative cytogenetic and T-cell surface marker tests may reflect undetectable levels due to analyzing procedure or sensitivity [7]. Some clones may be too small to be detected by conventional techniques, and some L-HE patients may have been in the early stage of a low grade clonal T-cell proliferation undetectable by available techniques, which become overtly clonal with the passage of time [2]. In the end we diagnosed our case as L-HE.

Glucocorticoids (GC) may induce eosinophil apoptosis and modulate T-cell function by inhibiting production of T-helper cell 2 (Th2) cytokines and IL-2 [8], whereas the influence on abnormal T cells is variable. In most cases, the proportion of CD3+CD4+ aberrant T-cells is not affected by GC. IL-2, in combination with IL-4, reduces both glucocorticoid receptor binding affinity and inhibition of T-cell proliferation in GC resistant patients [11]. Subpopulations of CD4+ T-cells that secrete Th2 cytokines and IL-2 have been reported to be less responsive to the inhibitory effects of GC, enabling them to continue proliferating [12]. IL-8, which generally acts as a leukocyte chemotactic factor, is reported to play an important role in eosinophilic proliferation, like the Th2 response, and exacerbates L-HE [13]. Some additional mechanism related to serum IL-8 might also affect the steroid response.

From the perspective of steroid resistance, steroid-sparing agents are essential. The main therapeutic mechanism of Cy is suppression of T-cell proliferation by interfering with the intracellular signaling pathways which lead to inflammatory cytokine synthesis, including Th2 mediated cytokine production [3]. One other mechanism depends on the inhibition of P-glycoprotein (P-gp) function, reducing the lymphocytic cellular efflux of steroids which are substrates of P-gp. As a result, Cy increases the steroid accumulation in lymphocytes, leading to the decrease of eosinophilopoietic cytokines synthesis [14]. IFN-α is antagonistic to Th2 response and decreases the production of IL-5 [15], thereby inhibiting eosinophil proliferation [16]. We were unable to achieve a sufficient steroid-sparing effect even from these agents. Anti-IL-5 antibody approaches have been studied in HES based on the cytokines’ role as a differentiation, activation, and survival factor for eosinophils. It inhibits binding of IL-5 to its receptor expressed on eosinophils, and represents a GC-sparing effect in L-HE patients [15].

HE caused by aberrant T-cell population has a risk of malignant progression toward lymphoma [17]. Accumulation of cytogenetic changes in T-cells and proliferation of lymphocytes with abnormal phenotypes have been observed with progression to lymphoma [9]. We interpreted the progressive refractoriness to steroids and acute aggravation of tumor-like lesions in the lung fields and intestinal tract as early signs of malignant transition. In some HES patients, CD30+ T-cells present in activated lymphocytes [18] are histologically observed predominantly in their skin lesions, and were reported to occasionally develop into malignant lymphoma [19]. There is also a case report about CD30+ T-cell lymphoma in a HES patient with systemic organ damage involving skin, lung, and digestive tract [20], which is similar to our case. Therefore, we considered that the next course of treatment in this patient would be cytotoxic chemotherapy or bone marrow transplantation. We should pay attention to any clinical manifestations suggesting malignant development of HES, such as lymph node swelling, steroid resistance or elevated serum LDH level, and modify the treatment regimen accordingly to avoid therapeutic delay.

CONFLICT OF INTEREST: None

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