Hypereosinophilic syndrome (HES) has generally been defined as a peripheral blood eosinophil count greater than 1500/mm³ and may be associated with tissue damage. Imatinib is customarily used as the first-line therapy for HES with gene abnormalities, such as PDGFRA or PDGFRB. We presented a case where the patient was diagnosed with HES, with PDGFRB rearrangement. The patient began an imatinib regimen after diagnosis and then developed resistance to imatinib. The combination of dasatinib, methylprednisolone and hydroxyurea was administered to the patient as the salvage therapy.

1. Introduction

The eosinophilias encompass a broad range of nonhematologic (secondary or reactive) and hematologic (primary, clonal) disorders with potential for end-organ damage. Hypereosinophilic syndrome (HES) has generally been defined as a peripheral blood eosinophil count greater than 1500/mm³ and may be associated with tissue damage. Overall, HES is a rare disease with an incidence of approximately 0.036 per 100,000. After exclusion of secondary causes of eosinophilia, diagnostic evaluation of primary eosinophilias relies on a combination of morphologic review of the blood and marrow, standard cytogenetics, fluorescent in situ hybridization, flow immunocytometry, and T-cell clonality assessment to detect histopathologic or clonal evidence for an acute or chronic myeloid or lymphoproliferative disorder.

The classification of eosinophilic diseases was revised in the 2008 World Health Organization categorization of myeloid neoplasms. In recognition of the growing list of recurrent, molecularly defined primary eosinophilias, a new major category was created, “Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of platelet-derived growth factor receptor alpha (PDGFRA), platelet-derived growth factor receptor beta (PDGFRB), or fibroblast growth factor receptor 1 (FGFR1)” (Table 1). The success of imatinib in cases of chronic myelogenous leukemia (CML) led to its empirical use in patients with HES who exhibited signs suggestive of a myeloproliferative disorder since 2001. However, the effect of imatinib varied with gene abnormalities in treating HES.

As we know, some patients with CML develop resistance to imatinib. In prospective cohorts, imatinib-treated FIP1L1-PDGFRA-positive myeloid neoplasms were evaluated and resistance of imatinib was rarely reported. Herein we have presented a case diagnosed as HES with PDGFRB rearrangement that subsequently developed resistance to imatinib.

2. Case presentation

Initially, the 39-year-old woman presented to our facility with fever, skin rash, and pneumonitis in February 2005 (Fig. 1). Her hemogram showed a WBC of 30,100/mm³, Hb 13.7 g/dl, PLT 303000/mm³, seg 61%, lym 21%, mono 10%, and eos 8%. Her pulmonary function test displayed normal ventilator function and moderate reduction of gas exchange in May 2005. We had administered pulse therapy (steroid) for 3–4 months but her eosinophil counts remained persistently high. Then, she had been noted as persistent hypereosinophilia (absolute eosinophil count >1500/mm³) for more than 6 months. She received a lung biopsy...
in January 2006, wherein the pathology revealed increased eosinophils in the capillaries of the alveolar walls. She received both bone marrow examination and bone marrow cytology, which showed hypercellularity of approximately 80%, an M/E ratio of 4/1, no excess blasts, no dysplastic changes, and eosinophilia of about 8% in November 2007. Subsequent to review of gastrointestinal stromal tumors, her fusion gene was detected as t (5; 14) KIAA1509-PDGFRB by PCR and the karyotype was t (3; 16) (p13; q24), −16, −18, +mar. Lab data were noted normal-range ESR 8 mm/h and high-level IgE 1168 kU/L. Her abdominal sonogram detected splenomegaly with long axis of about 12.8 cm. At that time, we searched associated journals about HES for diagnosis.5 In the next year, according to the 2008 World Health Organization (WHO) classification of myeloid malignancies, the diagnosis of this patient was revised as “myeloid neoplasms associated with PDGFRB rearrangement”. Besides, pneumonitis may be recognized as end-organ damage (Fig. 2).

After diagnosis, the patient still complained of shortness of breath and started to take imatinib 200 mg per day in January 2006 and methylprednisolone 8 mg per day in November 2007 (Fig. 3). This combination had lasted for 4 months, after which she then kept using imatinib. Subsequent computer tomography (CT) of the chest revealed gradual regression after imatinib use (Fig. 4).

Prior to admission to our facility, her disease had been stable for 6 years (2008–2013). During this period, the fusion gene PDGFRB had not been detected (from May 2008 through August 2012). Unfortunately, she suffered from progressive dyspnea and a CT of her chest also revealed progressive pneumonitis in October 2013 (Fig. 5). Her WBC count was elevated to 13,400/mm³ (AEC 817/mm³). However, her fusion gene PDGFRB was still not detected. We increased the dose of imatinib to 400 mg per day in November 2013. However, the symptoms did not improve. We arranged for a re-biopsy of her lung lesion to investigate other possible etiology in April 2014. The pathology still revealed “eosinophilic pneumonia with cellular interstitial lymphoid cells infiltration”. Due to the limitation of our laboratory, we could not detect the T674I mutation. Then, we prescribed nilotinib 300 mg per day exclusively to replace imatinib in June 2014. However, this change of drug regimen still only produced a poor result. Her lung lesions were getting worse and WBC count also increased to 21,400/mm³ (AEC 2268/mm³). We rechecked the fusion gene PDGFRB and the result was negative. Dasatinib 70 mg per day was administered to replace nilotinib in September 2014. After 2 months, the disease activity did not subside. Due to the patient’s economy and choice, we decided to use the combination of dasatinib 50 mg per day, methylprednisolone 8 mg per day, and hydroxyurea 1000 mg per day. Thereafter, her symptoms improved and AEC also decreased. A successive CT of the chest was also consistent with clinical improvement (Fig. 6).
3. Discussion

Clinically, HES may be separated into two subgroups: HES with, and HES without gene abnormality such as PDGFR, PDGFRB, or FGFR1. The standard therapy of HES without gene abnormality is steroid; by contrast, the first-line therapy of HES with gene abnormality is imatinib.

Although in-depth and durable molecular responses occur with imatinib, discontinuation of the drug can lead to relapse. In the French series, imatinib was stopped in 11 patients - 6 of those patients subsequently relapsed. According to these studies, we may presume that imatinib could suppress abnormal clones, but not clear them out. In contrast to CML, very few cases of acquired imatinib resistance have been reported with almost 10 years of experience in treating FIP1L1-PDGFRA-positive disease. Most of the cases have involved the T674I mutation within the ATP-binding domain. The T674I mutation is analogous to the T315I BCR-ABL mutation in CML which confers resistance to the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib.

The salvage therapy of imatinib-resistant HES has remained unclear so far. In this case, our laboratory could not provide the test detecting the T674I mutation. According to the study of David M. et al, imatinib with 400 mg per day could elicit durable hematologic and cytogenetic remissions. However, this patient developed resistance to imatinib 400 mg per day. Then, dasatinib 70 mg per day was prescribed but her symptoms did not improved. Following the patient’s insistence of dasatinib 50 mg per day, we tried the combination therapy with dasatinib, steroid, and hydroxyurea. Fortunately, this regimen was effective as to this patient. We did not answer the mechanism of this salvage therapy and just provided a feasible regimen in treating imatinib-resistant HES.
Fig. 4. A successive CT of the chest showing regressive changes in September 2008 (After imatinib 200 mg/day by 1 year).

Fig. 5. A CT of the chest showing patchy ground glass opacities at lingual segment of LUL and LLL of lung, increased infiltration in the RLL of the lung when the disease deteriorated in October 2013. (After imatinib 200 mg/day for 6 years and before imatinib 400 mg/day).
References