CASE REPORT

Response of Complex Undefined Hypereosinophilic Syndrome to Treatment with Imatinib

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Abstract

Hypereosinophilic syndromes (HESs) include potentially lethal multisystem disorders characterized by eosinophilic infiltration of a variable spectrum of target organs, predominantly the skin, heart, lungs, gastrointestinal tract, and nervous system. Based on recent advances in molecular and genetic diagnostic techniques and increasing experience with differences in clinical features and prognosis, subtypes have been defined, including “myeloproliferative-HES”, “lymphocytic-HES”, “familial eosinophilia”, “overlap HES”, “undefined HES” (“complex undefined HES”, “simple undefined HES”, “episodic undefined HES”) and “eosinophil associated diseases” (such as Churg-Strauss syndrome). HES should be kept in mind in the differential diagnosis of eosinophilic lung diseases especially in patients with peripheral eosinophilia and pulmonary infiltrates. Corticosteroids represent an effective firstline approach to decreasing eosinophil counts in the majority of cases. Imatinib might be used for corticosteroid nonresponders. We herein report a patient with “complex undefined HES” who had disease resistant to corticosteroids, but who had a significant response after treatment with imatinib.

KEYWORDS: Hypereosinophilic syndrome, Churg-Strauss syndrome, complex undefined hypereosinophilic syndrome, imatinib

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INTRODUCTION

After excluding secondary factors that can cause hypereosiniphilia, hypereosiniphilia is evaluated under hypereosiniphilic syndrome (HES). The criteria for hypereosiniphilic syndrome are as follows: 1) eosinophile over 1500/mm³; 2) persistent eosiniphilia (does not have to last more than 6 months) or organ damage/dysfunction; 3) exclusion of secondary reasons of eosiniphilia [1]. HESs are examined under six separate headings including “myeloproliferative –HES (M-HES)”, “lymphocytic-HES” (L-HES), “familial eosiniphilia”, “overlap eosiniphilic HES”, “undefined HES”, and “eosiniphil associated diseases” [2]. Undefined HES is also examined under three separate headings including “complex undefined HES”, which is symptomatic organ infiltration associated with eosiniphilia; “simple undefined HES”, where the disease progresses with only eosiphilia elevation without organ involvement; and “episodic HES” where the disease progresses with cyclic angioedema and esoniphilia. Recently Churg-Strauss Syndrome (CSS) also named as “Eosiniphilic granulomatosis polyangiitis” has been examined under the sub-group of esoniphilia related HES diseases and is a necrotizing systemic vasculitis that affect small-medium diameter blood vessels [3,4].

Complex undefined HES is an ecarttaion diagnosis, which can progress with multiple organ involvement and mimic many diseases. Therefore, a very extensive differential diagnosis needs to be made. CSS, one of the eosiniphilic lung diseases, must be considered in differential diagnosis since treatment and prognosis can be different. This study presents a case that was referred to our clinic with CSS diagnosis but received “complex undefined HES” diagnosis.

CASE PRESENTATION

A 40-year-old male patient was given inhaler as a result of asthma diagnosis in different clinics to which he applied with complaints like cough and dyspnea; however, these treatments were not beneficial at all. Due to the detection of peripheral eosiniphilia, asthma-like symptoms, pulmonary nodules on thoracic computed tomography (CT), and eosiniphilia in transbronchial biopsy, the patient received CSS diagnosis and was started on methylprednisolone 40 mg/day which was gradually decreased. Owing to the fact that there was no ameliorartion in his symptoms,

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methotrexate 15 mg/day was added to the patient's treatment one year later. The patient had been using methylprednisolone (24 mg/day) and methotrexate (10 mg/day) before he applied to our clinic. The patient who had not had regression in his complaints and had developed corticosteroid side effects (myopathy, cushingoid appearance) applied to our clinic. The patient who described dyspnea with mild effort had a cough that hit during daytime and increased with exercise. Patient history did not include allergic asthma, rhinitis, nasal polyposis, and atopic dermatitis. The patient did not describe any bruxing, itching in the anal region, consuming raw food, and suspicious travel. The patient did not have drugs, food, bee allergies, did not smoke, and had not undergone surgeries. There was no characteristic to be detected in the patient's and family history. Blood pressure at the time of admission was 130/80 mmHg, respiratory rate was 20/min; pulse was 90/min; and saturation at room temperature was 95%. Respiratory and other system examinations were normal. Blood eosinophilia ratio of the patient with mild leukocytosis was found as 37% (4280/mm³). Anemia and thrombocytopenia were not detected. Bilateral bronchovascular shadows became evident on the posteroanterior lung graphy.

Since symptoms of cough and dyspnea continued in our case and due to eosinophilia, examinations were conducted towards the etiology of hypereosinophilia. Microscopic investigations of the faeces were negative. Prick tests carried out with food (mutton, chicken, apple, orange, banana, strawberry, peanut, hazelnut, tomato, walnut, lemon, potato, kiwi, rye flour, wheat flour, cow milk, cocoa, egg white, egg yolk, shrimp, fish) and aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Betulaceae*, *Salicaceae*, field pollen, compositae, tree pollen, grain pollen, *Penicillium*, *Aspergillus*, *Cladosporium*, *Alternaria*, cockroach, cat, dog, horse) (Stallergenes, France) were detected negative. Mild restrictive pattern was present in pulmonary function tests and there was no reversibility. Routine laboratory tests were also normal. C-reactive protein, rheumatoid factor, anti-cyclic citrullinated peptide, sedimentation, aspergillus-specific IgE, anti-nuclear anticore, anti-neutrophil cytoplasmic anticore, anti-dsDNA,

creatine kinase, Troponin T, immunoglobulins were detected normal. Anti-HIV, hepatitis marker, cyst hydatid IHA/IFAT, amoebiasis IFA were negative. Only vitamin B12 was high (1291 pg/mL).

Milimetric nodular appearances with ground glass densities in upper lobes were determined on thoracic CT (Figure 1a). Pathological findings were not detected on paranasal CT and upper and lower abdomen CT. Echocardiography was normal. Eosinophilia-rich inflammatory cells were detected in transbronchial lung biopsy. Numerous eosinophilic granulocytes were present in bone marrow biopsy. Increase in blast and malignant infiltration were not detected (Figure 2). JAK-2 mutation and Philadelphia chromosome were negative. Lymphoreticular malignancies were excluded. Solid organ malignancy was not considered in the patient in whom no primary malignancies were detected. Due to the fact that Vitamin B12 value was high, advanced molecular tests were asked for HES variant sub group analysis. FIP1-like1 (FIP1L1) and platelet-derived growth factor receptor (PDGFR) α mutation were found negative.

Our case received a diagnosis of complex undefined HES since eosinophilia-rich cellularity compatible with HES was detected in bone marrow biopsy, necrosis and eosinophilic infiltration where granulomatosis reaction was not present was detected in lung biopsy, and other diagnoses that could cause eosinophilia were eliminated. Our case did not respond to corticosteroid treatment and imatinib mesylate 400 mg/day was started. Clinical response was achieved in the first two weeks of treatment. As all complaints disappeared and eosinophil levels returned to normal in the first month, the dosage was decreased to 100 mg/day. Radiologic improvement was present on thoracic CT (Figure 1b). The patient still receives imatinib 100 mg/day in the first year of treatment. No side effects related to imatinib has been observed. Our case was presented with a review of the literature after receiving his consent.

DISCUSSION

Hypereosiniphilia has a wide range of evaluation areas from parasitic diseases to drugs, leymphoreticular malignancies,

Figure 1. (a) Centrilobular ground glass nodules in upper lobes of the lung before imatinib treatment, (b) Regression is seen in centrilobular ground glass nodules 1 year after imatinib treatment.

Figure 2. Bone marrow biopsy is cellular and dominance attracts attention in myeloid elements mostly eosinophilic series (x400, HE)

solid organ malignancies, CSS, and ABPA [5]. Practical approach consists primarily the inquiry of history of drug use that could cause eosinophilia and the history of parasitic infection. If there is history of drug use, it should be stopped. If these conditions do not exist, other secondary reasons for hyperesinophilia should be looked into [5]. Microscopic investigations of the faeces were carried out six times on separate days and serologic tests were asked for parasitic infections. The test results were negative. Furthermore, parasite or history of drug use that could cause Löffler syndrome was not present.

Patients with asthma should be evaluated for CSS and ABPA in case of very apparent eosinophil [6,7]. Six criteria have been established by ACR for the diagnosis of CSS syndrome, including 1) Asthma; 2) Eosinophilia > 10%; 3) Mononeuropathy or polyneuropathy; 4) Pulmonary infiltrates on radiologic imaging; 5) Paranasal sinus pathologies; and 6) Pathologic amplifying where extravascular eosinophilic infiltrations are shown [8]. Carrying four or more of these criteria enable CSS diagnosis in patients who have already been proven to have vasculitis histopathologically [9]. Our case carried three of the ACC criteria (eosinophilia > 10%, eosinophilic tissue infiltration and ground glass nodules on thoracic CT) and did not have a histopathological diagnosis compatible with vasculitis. Moreover, CSS prodromal period findings were not present. Hence, CSS was not considered in our case. The diagnosis of ABPA, one of the causes of hyperesinophilia, was excluded due to the normal value of T. IgE, having not detected aspergillus sensitivity on skin prick test, and negative value of aspergillus-specific IgE. A probable solid organ malignancy that could cause hyperesinophilia was not considered in our case who did not have any complaints regarding weight loss and loss of appetite, on whose radiologic examinations, a primary malignancy was not detected, and whose sedimentation and tumor markers were normal. Blood eosinophilia can accompany organ-specific eosinophilic diseases, such as chronic eosinophilic pneumonia (CEP), eosinophilic gastroenteritis, and some dermatological disorders [5]. Dermatological and gastrointestinal involvement was not present in our case. Having not

detected radiological findings compatible with CEP and having had no corticosteroid response had us move off from CEP diagnosis. "Familial HES" was not considered since there was no family history of HES. Myeloproliferative and lymphoproliferative malignancies were ruled out as a result of peripheral smear, bone marrow biopsy, flow immunocytometry, and cytogenetic investigations.

If the underlying reason of eosinophilia is not detected, advanced diagnostic tests should be asked for to detect HES variants [5]. In most M-HES patients, due to the interstitial deletion on the 4q12 chromosome, FIP1-like1 (FIP1L1) and platelet-derived growth factor receptor (PDGFR) α genes are caused to fusion, which results in the activation of tyrosine kinase [10]. FIP1L1-PDGFR α mutation was detected negative in our case. However, carrying four or more of the following eight characteristics in FIP1L1-PDGFR α negative HES cases is evaluated under: 1) the presence of dysplastic eosinophils on peripheral smear; 2) having serum vitamin B12 level over 1000 pg/mL; 3) having serum tryptase level over 12 ng/mL; 4) anemia, thrombocytopenia or the association of both; 5) hepatosplenomegaly; 6) over 80% cellularity in bone marrow biopsy; 7) the presence of dysplastic mast cells in bone marrow (being 25% more than spindle-shaped mast cells); 8) Myelofibrosis (having antireticuline anticore staining in bone marrow biopsy) [2]. M-HES diagnosis was not considered for our case since he did not carry the criteria apart from Vitamin B12 elevation.

L-HES is characterized with nonmalignant expansion of T cell population that can produce eosinophilopoietic cytokine. IgE, IgM and IgG are generally detected high in L-HES cases [11]. Other frequently seen characteristics include 1) skin involvement; 2) frequent presence of history of atopy; 3) glucocorticosteroid response is generally very good [12]. L-HES variant diagnosis was also not considered in our case as atopy was not detected, immunoglobulins were normal, and particularly there was no corticosteroid response in our case. After having excluded all secondary reasons that could cause hyperesinophilia and other diseases ranking among the sub-groups of HES, our case was diagnosed with complex undefined HES.

Although all organs theoretically have the potential to infiltrate with eosinophils, cardiovascular, pulmonary, skin, nervous, and gastrointestinal systems are the most frequently affected and pulmonary involvement is seen around 50% [13]. Only pulmonary involvement was present in our case.

In FIP1/PDGFR α negative HES cases, first choice of treatment is corticosteroids. In cases that do not respond to corticosteroid treatment and those who cannot use this drug due to its side effects, many cytotoxic drugs have been used instead. Hydroxyurea is the most studied among all. However, its use as monotherapy shows limited benefit. Moreover, therapeutic effectiveness of effective immunomodulator treatments on Th2 type cytokines (IL5, IL-4) and treatments like cyclosporine and alemtuzumab on IFN- α have been shown in selected cases [2,11,14]. Imatinib mesilate is a tyrosine kinase inhibitor. It is used in the treatment of PDGFR α -related HES

that causes the activation of tyrosine kinase by generating the fusion of FIP1/PDGFR α genes. Its use on PDGFR α negative HES cases is limited [4]. However, imatinib can be considered second choice treatment in cases with no response to corticosteroid [5,15].

In FIP1/PDGFR α positive HES cases, response to imatinib is very quick. Eosinophil generally regresses to normal values within 1 week, and symptoms and findings improve in 1 month. The dosage of imatinib is decreased to 100 mg/day when eosinophilia and its symptoms are under control. In FIP1/PDGFR α negative HES cases, a higher initial dose of 400 mg/day can be needed [2]. Despite corticosteroid treatment, clinical response could not be received and eosinophil levels did not regress in our case, which led us to start imatinib treatment. After this treatment, an apparent clinical response was achieved in one week and eosinophils regressed to normal values.

In conclusion, complex undefined HES is an ecartation diagnosis. Its differential diagnosis should be made with eosinophilic lung diseases which are pulmonary disease groups that progress with particularly peripheral eosinophilia or tissue infiltration. Imatinib should be definitely kept in mind in the treatment of these patients that do not respond to corticosteroid treatment.

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