Response to Corticosteroids and Cytotoxic Drugs in a Case of Idiopathic Hypereosinophilic Syndrome with Predominantly Elevated Eosinophils and Multiple Clinical Manifestations

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Abstract In the present case study, a 42-year-old Chinese woman fulfilling the WHO criteria for idiopathic hypereosinophilic syndrome (IHES) who exhibited clinical manifestations of eosinophilic infiltration of multiple tissues including the lungs, heart, central and peripheral nervous system, gastrointestinal tract, spleen, liver and unexplained clinical findings is described. Laboratory investigations revealed the topmost white blood cell and eosinophil that were $150 \times 10^9/L$ and $136 \times 10^9/L$ (90.6 %), respectively. To our knowledge, such a large number of eosinophils has rarely been reported, and all reactive causes of hypereosinophilia were excluded. Treatment with cytotoxic chemotherapy, prednisone and dexamethasone was not beneficial. The patient showed a remarkable hematological response when methylprednisolone pulse therapy was initiated when progression of respiratory symptoms occurred, but without clinical remission. The patient subsequently died. We consider that her critical organ damage and poor prognosis were related to the large number of eosinophils and delayed effective anti-eosinophilic therapy after severe organ damage occurred. This case highlights the clinical importance of methylprednisolone pulse therapy which should be initiated without delay once the diagnosis of IHES is made.

Keywords Hypereosinophilic syndrome · Chemotherapy · Corticosteroids · Clinical studies

Introduction

Idiopathic hypereosinophilic syndrome (IHES) is characterized by sustained overproduction of eosinophils which results in infiltration of multiple tissues, and is diagnosed after exclusion of reactive eosinophilia. Because there are only a limited number of published reports on IHES, the clinical features and prognosis of IHES remain unclear, and standard treatment has not been established. Patients who have multiple clinical manifestations and markedly elevated eosinophils in addition to hematologic derangement are rarely reported. We report a case of IHES to elucidate the clinical characteristics and treatment outcome.

Case Report

A 42-year-old Chinese woman was admitted to our hospital on the 14th of October 2008 due to a 1-month history of persistent fever, progressive weakness in the left leg, recurrent nausea, vomiting, abdominal distention, a 2 day history of productive cough and dyspnea. Rhonchi were heard bilaterally all over the lung fields.

Blood tests showed an elevated white blood cell (WBC) count of $59.1 \times 10^9/L$ with an absolute eosinophil count of $48.1 \times 10^9/L$. Abnormalities present on routine electrocardiography (ECG) were non-specific ST-segment and T-wave changes. Cardiac enzymes were elevated and the LDH level was 323 U/L and hydroxybutyrate dehydrogenase (HBDH) was 231 U/L, the creatinine kinase (CK) level and CKMB fraction were normal. Thyroid function tests yielded unremarkable results. No abnormalities were found on chest X-ray and computerized tomography (CT) scan of the head and chest. Abdominal CT showed mild hepatosplenomegaly.

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Bone marrow aspiration film (Fig. 1) demonstrated that the percentage of eosinophils was 58.5 % among other cells seen, with a shift to the left in eosinophil maturation, and no other abnormalities. Trephine biopsy section (Fig. 2) showed a marked increase in eosinophils. All reactive causes of hypereosinophilia were excluded. Stool microscopy for parasites was negative. All immunological screening results were negative. Tumor marker assays yielded normal findings. The hematological work-up excluded lymphocytic variant HES: no T cell population with abnormal phenotype in the bone marrow was observed, and normal peripheral blood T-cell subsets were present on flow cytometry. The karyotype of bone marrow aspirate was normal (46, XX), and molecular studies did not detect BCR/ABL and FIPIL1-PDGFR fusion transcripts. The JAK2V617F point mutation was also absent.

The patient fulfilled the WHO criteria for IHES. Since the cause of fever, cough and dyspnea was suspected to be infectious, the patient was initially treated with antibiotics, without any improvement. As hypereosinophilia in peripheral blood was found, the patient was first treated with hydroxyurea alone (3 g/day), however, the peripheral blood eosinophil count increased progressively (Fig. 3a), and no clinical improvement was observed. After 9 days, the patient was subsequently treated with an intravenous bolus of cytarabine (25 mg/day for 3 days and 75 mg/day for 8 days) and homoharringtonine (2 mg/day for 7 days). Concurrently she was given prednisone at a daily dose of 40 mg for 6 days, followed by an intravenous bolus of dexamethasone 10 mg daily for 5 days. Treatment with prednisone, dexamethasone and chemotherapeutics only resulted in a transient and mild clinical improvement in neurological disturbance and respiratory symptoms with normalization of body temperature, but did not reduce the eosinophil count in peripheral blood. Both the peripheral

Fig. 1 Bone marrow aspiration film showing an elevated number of mature eosinophils, Wright-Giemsa stain, 100 × 10

Fig. 2 Trephine biopsy section showing a marked increase in eosinophils, hematoxylin–Giemsa–eosin stain, 40 × 10

white blood cell count and eosinophil count markedly increased to $150 \times 10^9/L$ and $136 \times 10^9/L$, respectively (Fig. 3b). Deterioration in her condition was observed several days later, and she was observed to have the recurrent behavior disorder, apathia. Shock occurred without an identifiable underlying cause, and vasopressor support therapy was effective. Fasting blood sugar level was low (2.8–3.9 mmol/L), while her appetite and diet were normal. Neurology, cardiology and endocrinology consultations confirmed that these findings were related to IHES. Concurrently her respiratory symptoms gradually returned and dyspnea progressively worsened, which were not controlled by bronchodilators. Repeat chest X-ray showed diffuse pulmonary microinfiltrates without cardiomegaly, and arterial blood analysis revealed hypoxemic respiratory insufficiency. Methylprednisolone pulse therapy of 1 g/day for 2 days and 240 mg/day for 3 days was given. The WBC count quickly decreased to $10.6 \times 10^9/L$ (Fig. 3c). Although the peripheral blood eosinophilia decreased, the patient died 25 days after admission.

Discussion

Diagnostic criteria have been established for IHES. They include persistent eosinophilia of $1.5 \times 10^9/L$ for at least 6 months or death before 6 months with signs and symptoms of organ dysfunction either directly related to eosinophilia or unexplained in a given clinical setting, and lack of evidence of other recognized causes of eosinophilia despite careful evaluation [1]. Based on the patient's medical record and laboratory data, this case fulfilled all of the main criteria for IHES, and is unique because of the markedly elevated peripheral blood eosinophil count. The total leukocyte count is usually less than $25 \times 10^9/L$, with

Fig. 3 The peripheral white blood cell count alteration of the patient during the 25 days after admitted

30–70 % eosinophils [2]. In our case, the topmost WBC and eosinophil count were $150 \times 10^9/L$ and $136 \times 10^9/L$ (90.6 %), respectively. To our knowledge, such a large number of eosinophils has rarely been reported. We ruled out chronic eosinophilia leukemia (CEL) in our case as no clonal aberration and eosinophilic blasts were detected. According to the WHO classification, patients with non-reactive eosinophilia are included in myeloproliferative neoplasms (MPNs). If a clonal aberration is present, it should be termed CEL, if no clonal aberration is detected, it is IHES [3].

Eosinophilic infiltration of tissues can potentially lead to irreversible, life-threatening organ damage. Any organ system may be involved, but the heart, central and peripheral nervous system, lungs and the skin are most frequently affected [2]. Pulmonary involvement is seen in 40–60 % of cases, and the most common respiratory symptoms are chronic persistent cough, productive sputum, wheezing and dyspnea [4]. Hemoptysis usually results from the margination of a large number of eosinophils in the lung vasculature, leading to eosinophilic accumulation [5]. Cardiac involvement occurs in about 60 % of patients with IHES [6], damage to the heart ranges from early necrosis to subsequent thrombosis and fibrosis, and usually leads to refractory heart failure. The nervous system is also one of the most commonly involved organs [7], and neurologic manifestations include: encephalopathy, peripheral neuropathy, and focal central nervous system deficits from emboli or hemorrhage [8]. Encephalopathy is characterized by memory loss, altered behavior, confusion, ataxia and so on, and may also result from microvascular eosinophilic occlusion, which a CT scan would not detect. Gastrointestinal involvement is characterized by a high level of eosinophils within the gastrointestinal tract [9]. Clinically, patients present with symptoms such as dysphagia, vomiting, abdominal pain and diarrhea. In our patient, the spectrum of clinical manifestations was wide, involving many organs and systems: the lungs, heart, central and peripheral nervous system, gastrointestinal tract, spleen and liver. She also experienced hypoglycemia and shock,

which were unexplained in the given clinical setting. Previous reports have shown that the extent of tissue eosinophilic infiltration does not usually correlate with peripheral blood eosinophilia [1, 2]. Extremely high leukocyte counts ($>90 \times 10^9/L$) develop in some patients and are associated with a poor prognosis [10]. We suggest that such a large number of circulating eosinophils may contribute to the progression of microvascular eosinophilic occlusion, leading to multiple organ damage and a poor prognosis. In particular, pulmonary and cardiac infiltrates have a very poor prognosis.

Until recently, no specific or efficient therapy was available for IHES. Cytotoxic chemotherapy and corticosteroids are used in order to lower the eosinophil count, reduce the overall WBC count and improve symptoms [11]. In some reports, conventional cytotoxic chemotherapy such as hydroxyurea, vinca alkaloids, vincristine, 6-thioguanine (6TG), etoposide, cytarabine, and 2-chlorodeoxyadenosine, with or without corticosteroids, provided long-lasting results in IHES patients [4, 5, 12–15]. In other reports, cytotoxic agents provided only limited disease control and quickly become ineffective [1, 16]. The findings in the present case supports the latter, in particular hydroxyurea did not produce any clinical and hematologic improvements: symptoms persisted, and WBC and eosinophil counts increased. Treatment with chemotherapeutics including cytarabine and homoharringtonine combined with corticosteroids (prednisone and dexamethasone) only resulted in a transient and mild clinical improvement, but did not lower eosinophil counts.

The treatment of patients with IHES mainly consists of corticosteroids [10]. Some available published case reports suggest that treatment with prednisone or deflazacort may be effective [17–22]. Our patient showed no hematological response to prednisone or dexamethasone. Some reports have shown that methylprednisolone pulse therapy [23, 24] is effective in patients even with life-threatening organ damage. Previous case reports have demonstrated a marked reduction in eosinophil count in parallel with further clinical improvement. In our patient, methylprednisolone

reduced the absolute eosinophil count, and showed a remarkable and rapid hematological response when progression occurred despite prednisone, dexamethasone and antimetabolite therapy. However, the respiratory symptoms were uncontrollable. The prognosis for IHES patients is thought to be related to treatment with corticosteroids as appropriate treatment with corticosteroids is critical for a good outcome. Patients with IHES who experience corticosteroids-induced eosinopenia have a better prognosis than those whose eosinophilia is unaffected by corticosteroids [10]. Some reports suggest that treatment with corticosteroids in the early stage may prevent further progression [25]. Therefore, we suggest that methylprednisolone pulse therapy should be initiated without delay once a diagnosis of IHES is made in order to avoid permanent, structural damage.

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