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REVIEW ARTICLE

Heart Failure Due to Idiopathic Hypereosinophilic Syndrome in Pregnancy: A Case Report and Review of the Literature

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ABSTRACT

Background: Hypereosinophilic syndrome is defined as the sustained overproduction of eosinophils leading to the dysfunction of one or more organs. Most of the deaths associated with Hypereosinophilic syndrome are related to cardiac involvement.

Case Presentation: We present the case of a 32-year-old woman who became pregnant during her follow-up period for her diagnosis of HES with cardiac involvement. She was treated successfully with a combination of IFN-alfa and prednisolone. She underwent an elective C-section at 39 weeks and delivered a healthy infant weighing 3400g. The patient died due to a complicated intra-abdominal infection secondary to colon perforation at 8 years of illness and 4 years of giving birth.

Conclusion: We reviewed the literature on the best treatment modalities for this challenging issue. Management of idiopathic HES causing severe heart failure during pregnancy can be achieved using steroids and interferon-α.

Key Words: Idıopathic Hypereosinophilic Syndrome; Pregnancy, Heart Failure

Introduction

Eosinophilia is commonly seen in clinical practice and is defined as eosinophil counts greater than 0.5 x 10^9/L. It is arbitrarily divided into mild (0.5-1.5 x 10^9 /L), moderate (1.5- 5 x10^9/L), and severe (>5 x10^9/L)[1]. Hypereosinophilia has generally been defined as a persistent eosinophil count of >1.5 x10^9 /L. Hypereosinophilic syndrome (HES) is a rare and critical complication of moderate to severe eosinophilia.

HES was first described by Chusid et al. in 1975[2]. In 2012, a panel of experts reached a consensus on terminology about HES[3]. This definition requires 1) hypereosinophilia (eosinophil count >1.5 x 10^9/L for at least 4 weeks or longer), 2) evidence of related organ dysfunction, and 3) the absence of secondary causes of tissue damage.

HES is a clinical picture that needs both knowledge and experience to determine its etiology and treatment[1]. Although the incidence and prevalence of HES are not known exactly, it is an extremely rare (the age-adjusted incidence rate: ~0.4 cases per 1 000 000) hematologic disorders[1,4]. Its clinical manifestations and course may vary from indolent to rapidly fatal. Skin, lung and gastrointestinal system are the most common organ involvements (~20%); however, cardiac involvement is <5% at the time of diagnosis[5]. Throughout the course of the disease, cardiac involvement of HES may be present in ~20 % of patients and can be a major cause of morbidity and mortality[2,5].

Pregnancy is a challenging condition in patients with HES with cardiac involvement. We reviewed the literature on best treatment modalities for this challenging issue with our successfully managed pregnant patient.

Case Presentation

In August 2012, a previously healthy 32-year-old woman presented with a 90-day history of daily fevers, sweats, dry cough, progressive dyspnea (including dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea), fatigue, and severe colitis associated with frequent loose (≥6 per day), bloody stools, colicky abdominal pain, urgency, and tenesmus. She reported no medical, relevant travel history, contact with tuberculosis, and high-risk sexual behavior.

On examination, she was unwell. Axillary temperature was 38°C, pulse 110 beats per minute, blood pressure 110/70 mm Hg, and respiratory rate 25 breaths per minute. Cardiac examination showed elevated jugular venous pressure, lower extremity edema, S3 gallop, and extended expiration with bilateral pulmonary rales. The remainder of the examination was normal.

Laboratory results included leukocytosis (24 × 10^9/L) with 35% eosinophils (8,4×10^9/L), normocytic anemia (hemoglobin, 10 g/dL; and mean corpuscular volume, 80 μm^3), and thrombocytosis (620×10^9/L). No blast was observed in the peripheral blood smear.

Erythrocyte sedimentation rate (ESR) was 36 mm/h, C-reactive protein (CRP) 110 mg/L, and cardiac troponin I 0.41 (normal range, 0.01–0.1 ng/mL). Other blood tests including thyroid, kidney, liver, anti-neutrophil cytoplasmic antibodies, HIV, hepatitis B, and hepatitis C were normal. Tuberculin skin test and repeated stool samples for parasites and ova were negative. Her total IgE level was 2620 IU/mL (normal range <100 IU/mL).

Abdominal ultrasound demonstrated mild ascites. A chest radiograph was normal, but thoracic CT revealed ground-glass opacities, multiple patchy consolidations, and mediastinal LAP (≤3 cm). A transthoracic echocardiogram revealed a global hypokinetic left ventricle with EF 24%, moderate mitral-tricuspid failure, and pericardial effusion (25 mm). Endoscopic findings of the upper gastrointestinal and colon showed diffuse erythema and edema. Biopsies demonstrated significant eosinophilic infiltration in the stomach, duodenum, and colon.

Screening for all etiology of secondary or clonal eosinophilia including drugs, parasites, JAK2, FIP1L1-PDGFRA mutations, and serum total tryptase was negative. Based on the patient's clinical course and testing results, idiopathic HES-associated severe heart failure with reduced ejection fraction, and gastrointestinal, and pulmonary involvement were diagnosed.

The patient was offered an empirical trial of albendazole (400 mg twice a day for three days) without a response in blood eosinophilia. The patient was treated with high-dose prednisolone (50 mg/day; body weight 50 kg), combined with angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. We tapered the prednisolone over the next 6 months. She experienced complete remission of hypereosinophilia, and symptoms following the next few weeks of prednisolone treatment. CRP had decreased from 110 mg/L to 4 mg/L. The patient had a normal full blood count and ESR (15 mm/h). When we tapered prednisolone to 20 mg /day, hypereosinophilia and symptoms returned. Oral methotrexate (MTX) (15 mg weekly) was added to the treatment regimen. The patient re-experienced complete resolution following the next month of

prednisolone + MTX treatment. The patient was in remission for the following 18 months with maintenance prednisolone (10 mg/day) + MTX. However, she had recurrent symptoms after this period. We increased the dose of prednisolone (20 mg/day) and switched MTX to IFN-alfa (4 MU three times per week). She was in remission after a month. At the fifth month of her presentation, follow-up TTE showed dramatic recovery of systolic function (LV ejection fraction: 40%). When everything was under control with treatment, it was realized that she was 8 weeks pregnant in the 4th year of her follow-up. All medications were stopped but IFN-alfa and prednisolone.

The pregnancy was uneventful, and she underwent an elective C-section at 39 weeks and delivered a healthy child weighing 3400g. In May 2017, 2 months following delivery, follow-up TTE showed LV ejection fraction 25%. We restarted all the relevant drugs for her heart failure with reduced ejection fraction. We switched IFN-alfa to PEG-IFN alfa-2a. The patient took PEG-IFN alfa-2a (180 mcg once weekly) and prednisolone (5 mg/d) for 12 months before death. The patient died due to a complicated intra-abdominal infection secondary to colon perforation at 8 years of illness and 4 years of giving birth.

Discussion

Eosinophilia ($\geq 0.5 \times 10^9$ /L) occurs in a variety of diseases (e.g., allergic, infectious, inflammatory, and neoplastic disorders) [6] . Most patients with eosinophilia have mild eosinophil levels (0.5-1.5 $\times 10^9$/L). Eosinophil count is generally $<1.5 \times 10^9$/L in allergic diseases and $\geq 1.5 \times 10^9$/L in infections. The most common cause of eosinophilia in underdeveloped countries is tissue-invading helminthic infections, and the most common cause in developed countries is an allergic disease.

When eosinophilia level is found $\geq 1.5 \times 10^9$/L, assessing for associated end-organ damage is immediately necessary. Especially if extremely elevated eosinophil levels ($>100 \times 10^9$/L), leukocytosis and severe cardiac damage (e.g., acute heart failure) is detected, high-dose intravenous steroids (from 1 mg/kg of prednisone to 1 gram of methylprednisolone) should be started urgently[7]. Most patients respond to high-dose steroids and can stabilize within 1 week. After the urgency of organ involvement is resolved, the causes of HES should be investigated in detail.

HES is divided into 3 subgroups according to the pathogenetic mechanism leading to eosinophilia: primary (neoplastic), secondary (reactive) or idiopathic. Despite detailed investigations, the etiology can not be determined in 75% of HES cases and these cases are called idiopathic HES[8]. Eosinophilic myocarditis is a major cause of morbidity and mortality among patients with HES.

The clinical manifestations of myocarditis are arrhythmia, block, heart failure, and sudden cardiac death. Cardiac damage evolves through three stages; 1) an acute necrotic stage, 2) an intermediate thrombotic stage (characterized by thrombus formation on the damaged endocardium), and 3) a fibrotic stage (characterized by heart failure with reduced ejection fraction with ≤40 percent), and heart failure with preserved ejection fraction (with left ventricle ejection fraction >50 percent; known as diastolic heart failure). Management of idiopathic HES requires several considerations such as the degree of eosinophilia,end-organ dysfunction, and emergency of clinical picture[1-13].

The first recommended treatment in idiopathic HES is corticosteroid (prednisone: 20 to 60 mg daily) therapy. The dose of prednisone should be adjusted once the patient responds. If the patient can be kept in remission with a dose of more than 10 mg prednisone per day, steroid-sparing agent should be added. Interferon-alfa (conventional interferon alfa or pegylated interferon alfa) and mepolizumab can be used as steroid-sparing drugs. Mepolizumab is humanized IgG1 monoclonal antibody directed against interleukin-5 (IL-5), thereby reducing the production and survival of eosinophils[14,15]. Mepolizumab was first approved by the FDA in 2020 for idiopatic HES. Interferon alfa, in settings where mepolizumab is not available, is acceptable as second-line therapy for patients with idiopathic HES who do not respond to glucocorticoids. Current data (September 2022) on the safety of mepolizumab in pregnancy are insufficient.

To our knowledge, there are only 4 pregnant patients with HES reported in the English-language literature (Medline 1975-January 2022[9-12]). A case of an idiophatic HES with cardiac involvement in a pregnant patient is presented and the relevant literature is reviewed in this report.

This case will be the fifth report in the literature. Table I shows the features of all the pregnant cases with idiopathic HES. All but one were treated with prednisone, case number four and our case were combined with azathioprine and interferon-α, respectively. In case number two, clinical features of

the disease and hypereosinophilia disappeared during the pregnancy. Such a development may be a result of hormonal changes in pregnancy.

In conclusion; in patients with eosinophilia, a thorough step-wise evaluation is required to exclude neoplastic disorders. A detailed medical and travel history, a complete physical examination (e.g., rash, lymphadenopathy, and organomegaly), assessment of end-organ damage (e.g., chest radiography, echocardiogram, serum troponins, and oxygen saturation), and laboratory data should be completed promptly. Even in severe heart failure with a reduced ejection fraction of idiopathic HES, the management of pregnancy can be achieved using steroids and PEG-IFN-α. We think mepolizumab will also be a good option in steroid-refractory HES when sufficient safety data are available in pregnancy.

Table 1. Clinical features of pregnant patients with idiopathic hypereosinophilic syndromes

Reference, year	Case no / Age(y) /	Cardiac involvement (Echocardiogram)	Treatment / Delivery	Postpartum outcome
Albrecht et al. [9], 1997	1/22	No	Prednisone/ C-section (at 30 weeks)	At 10 months, The 2 male infants and mother well
Ault et al. [10] , 2009	2/30	No	No / Vaginal	The infant and mother well
Darki et al. [11], 2011	3/31	*Yes	Prednisone Vaginal	The infant and mother well
Pineton de Chambrun et al. [12], 2015	4/29	Yes Endomyocardial fibrosis with heart failure	Prednisone+azathioprine C-section (at 35 weeks)	At 6 months, the infant and mother well Echo and cardiac MR normal
Present case	5/32	Yes Heart failure EF 0.24	Prednisone+ PEG-IFN-alfa C-section (at 39 weeks)	At 2 months, the infant and mother well EF 0.25

* Normal EF and diastolic filling pattern and in the left ventricle, 2 echo dense structures

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