Hepatitis in Idiopathic Hypereosinophilic Syndrome: Report of An Unusual Case

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ABSTRACT

World Health Organization defines a rare diagnosis Idiopathic hypereosinophilic syndrome (HES) as a persistent eosinophilia for 6 months and resulting in end-organ dysfunction. Most of the patients present with nonspecific symptoms, while others will present with symptoms of the affected organs, commonly those involving the heart, skin, or nervous system. Gastrointestinal or liver involvement is estimated to affect up to one-third of patients with HES, although patients with clinically significant disease are limited to case reports. This is the first report of a patient presenting with idiopathic HES related hepatitis and achalasia. Hypereosinophilic syndrome has been reported to be associated with hepatic dysfunction; liver histology is mainly characterized by a diffuse eosinophilic inflammatory infiltrate. A 49-yr-old woman, diagnosed as a case of idiopathic hypereosinophilic syndrome with bone marrow and pulmonary eosinophilic infiltrates associated with peripheral eosinophilia, high IgE level developed features of chronic gastroenteritis, hepatitis, with a significant eosinophil component. She responded well to systemic glucocorticoid and Imatinib therapy with normalization of liver function tests within a few weeks.

Key words: Hypereosinophilic Syndrome, HES, Hepatitis

Introduction

Hypereosinophilic Syndrome (HES) is a heterogeneous group of rare leucoproliferative disorders. Criteria for diagnosis of HES is persistent blood absolute eosinophilia (1500/microliter or more) in the absence of secondary causes for eosinophilia with signs and/or symptoms of eosinophil mediated organ dysfunction1-7. Major causes of hypereosinophilia are allergies, atopy, helminth infections and drugs, which are described as secondary hypereosinophilia where the production of interleukin (IL)-3 and IL-5 that promote eosinophil proliferation. Lympho- reticular malignancy, some
solid tumours and some autoimmune diseases are less common causes.3–5 In primary hypereosinophilia, eosinophils are clonal and are derived from myeloid lineage and the main causes are myelogenous leukaemia or myelodysplastic syndromes.3,4 It a spectrum of diseases with variable organ involvement, clinical manifestations, and treatment response as well as prognosis.1 In HES any organ system may get involved but cardiac (58%), dermatological (56%) neurological (54%), and pulmonary (49%) involvement had been observed in more than 50% of cases.6-8 There are no confirmatory immunophenotypic markers for clonal hypereosinophilia; but these are highly indicative molecular markers.6 These are platelet-derived growth factor receptor alpha and beta (PDGFR and PDGFR), fibroblast growth factor receptor 1 (FGFR1), the c-abl oncogene (ABL1) and Janus kinase 2 (JAK2); the first three are related to t(8;13), t(5;12) and t(9;22) cytogenetic translocations.3,4,7 To meet the diagnostic criteria of hypereosinophilic syndrome, target organ damage, hypereosinophilia and absence of any other reason for organ damage are needed.6 Treatment options are glucocorticoids and nonsteroidal anti-inflammatory drugs according to symptoms, and tyrosine-kinase inhibitors directed against cytogenetic targets.3,7,8

Case presentation

A 49-year-old housewife was referred to our hospital with complaints of jaundice, pallor, fatigue, exertional dyspnoea, intractable itchy papular skin rashes all over the body for three months. She also complained of nausea and vomiting and 2-kg weight loss over the last one month period. Two months back with these complaints she was admitted into a teaching hospital and investigated thoroughly but no definitive diagnosis could be reached. She was treated symptomatically with steroid, improved and was discharged. Few days after when she stopped taking steroid, her symptoms reappeared. She had no past history of asthma, allergy, allergic rhinitis. Drug history was negative except for H1 and H2-receptor antagonists which she took during the last 2 months. She had no family history of liver or haematological diseases. Her vital signs were within normal range. Respiratory and cardiovascular systems and per abdominal examination were normal. Her investigation findings revealed haemoglobin level of 10.3 g/dl, white cell count of 11000/cmm of blood (neutrophils – 55%, eosinophils – 29%, lymphocytes – 10%) and platelet count of 200 x109/L. Peripheral blood picture showed microcytic hypochromic anaemia with eosinophilia. Platelet morphology was normal. Erythrocyte sedimentation rate was 57 mm in the 1st hour (normal <20). Total IgE was raised (1331.8 IU/ml), creatinine phosphokinase value was 32.9U/L (normal = 38-174U/L). Serum electrolytes, renal function tests and lipid profile were normal. CFT for filaria was negative. S. Bilirubin was 12.2 mg/dl, SGPT 333 IU/L, S. alkaline phosphatase 818 U/L, S. albumin 2.4 g/dL, PT 16 seconds. HBsAg, AntiHCV, AntiHAV, AntiHEV were negative. USG reports revealed Hepatitis with mild ascites. MRCP revealed Acute viral hepatitis with bilateral mild pleural effusion. Antinuclear Antibodies (ANA), Anti-Neutrophil Cytoplasmic Antibodies (ANCA), ANA, ANCA, C-ANCA, P-ANCA, Anti mitochondrial antibodies all were negative. Bone marrow aspirate showed micronormoblastic erythroid hyperplasia with increased eosinophil precursors. Bone marrow cytogenetics (FISH) for the mutant gene FIP1L1-PDGFR A, PDGFR B, FGFR1, CBFB were negative. ECG, echocardiogram, CXR (PA) view showed no abnormality.

Her diagnosis of idiopathic hypereosinophilic syndrome was made on the basis of clinical and haematological evidence. Patient was treated initially with oral steroids (1 mg/Kg/day), mast cell stabilizer and antihistamine. Skin rash, pruritus, eosinophilia and gastrointestinal symptoms had been resolved but reappeared after discontinuation of steroid and hepatitis yet was not improved. Then she was

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prescribed TKI (Imatinib, 100 mg/day) and hepatitis resolved. After six months, all symptoms reappeared while she was continuing Imatinib. So, the dose of Imatinib was increased to 400 mg/day but her symptoms were not improved, rather she developed serositis and thrombocytopenia. So, oral prednisolone (7.5 mg/day) was again added to Imatinib (100 mg/day) twice weekly. Her response was better with this combined drug therapy with normalization of liver function and other clinical features.

Discussion:

HES is a group of leucoproliferative disorders in which more than half of all patients have cutaneous involvement. In a minority of reports, skin involvement is the only manifestation of HES. Common cutaneous manifestations include pruritus, urticaria, dermographism, angioedema, erythematous papules, plaques, nodules and nonspecific rash etc. Our patient presented with pruritic skin lesions and persistent eosinophilia. After excluding other causes of reactive eosinophilia, a tentative diagnosis of HES with cutaneous and hepatic involvement was made.

Idiopathic HES is a systemic illness having the pathological hallmark of eosinophil infiltration in affected organs. Three cases of this syndrome were reported by Anderson in 1968 and he described the disease as hypereosinophilic syndrome. In 1975 definition of idiopathic HES was originally presented and was subsequently modified to include three criteria, with all being required for the diagnosis of HES. This Haste classic diagnostic criteria include (1) blood eosinophilia of >1500 cells/mm3 for 4 months, (2) no other apparent aetiologies for eosinophilia, and (3) evidence of end-organ dysfunction. However, as updated diagnostics now permits researchers to define autoimmune syndromes more rigorously, cellular clonality, and genetic mutations associated with HES, the number of cases defined as “idiopathic” is declining. Common presenting symptoms are fatigue, cough, dyspnoea, fever, myalgia, and rash. HES often involves the skin, heart, lungs, nervous system, and spleen.

Eosinophilic myocarditis is a major cause of morbidity and mortality among patients with HES which is characterized by myocardial infiltration with eosinophils and lymphocytes followed by myocardial necrosis. Heart failure, chest pain, arrhythmia, and cardiac thrombi include common cardiac presentations. As the disease progresses, chronic manifestations of restrictive cardiac disease secondary to widespread fibrosis can develop.2,3

There is significant variation in pulmonary involvement, but chronic, dry, insidious cough is a frequent complaint. However, eosinophilic infiltration into the pulmonary parenchyma may lead to focal or more widespread infiltrates. Pulmonary emboli are common in HES and result from endothelial damage secondary to local eosinophil degranulation and tissue necrosis. Because of the tendency toward thrombosis, anticoagulation is advised by some for this disorder. Pleural effusions can also occur.1,2

Corticosteroids are the treatment of choice for acutely ill patients with HES. Most patients are responding rapidly and there is a significant decrease in the number of circulating eosinophils. Reversible organ dysfunction usually improves quickly. To achieve long-term control of the disease has proven more difficult. As underlying aetiologies of HES are now discovered, targeted therapies may be beneficial. As for example, those patients with a FIP1L1/PDGFRA (Fip1-like 1/platelet-derived growth factor receptor alpha) mutation have been shown to benefit from treatment with tyrosine kinase inhibitors.4,5,6

Our patient markedly responds to steroids and Imatinib. Subsequently we shift to low dose maintenance steroids to prevent the persistent peripheral blood eosinophilia and itching. Patient showed a good response to combined therapy. Prognosis of HES has markedly improved now-a-days since it was first described (3-year mortality 75-88%) due to improved diagnostic methods, better understanding of pathogenesis, improved therapeutic measures and surgical
interventions for cardiac involvement. Nowadays, prognosis depends on the degree of cardiac involvement and the chance of development of haematological malignancies.

Conclusion:

Hypereosinophilic syndrome is a rare heterogeneous disease with multisystem involvement. It may even manifest with meningoencephalitis as a presenting feature. A high index of suspicion by the physicians in the background of persistent peripheral eosinophilia (after exclusion of secondary causes for eosinophilia) to diagnose and start the appropriate treatment is very important. The mortality of the condition is high with multi-organ involvement and early treatment can save lives.

References:


