Hypereosinophilic syndrome: A report of two cases and review of the literature

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ABSTRACT

Introduction:

Hypereosinophilic syndrome (HES) is a rare condition that is estimated to affect 1 out of every 1 to 2 per million people in the United States of America. HES is a heterogeneous group of disorders characterized by persistent eosinophilia with systemic organ dysfunction related either to eosinophilic infiltration or eosinophil-associated tissue damage.

Case Report:

We describe two female patients who presented with eosinophilia and hepato-splenomegaly and were diagnosed with HES. Both patients were negative for mutations in PDGFR-α but their presentations were otherwise consistent with the myeloproliferative variant of HES. Both patients were responsive to steroid therapy, but adverse effects necessitated discontinuation in one.

Discussion:

The pathophysiology of HES is based on endothelial damage with subsequent fibrosis, leading to infarction and thrombosis as a result of the release of eosinophil derived toxins from cells sequestered in organ systems. Criteria for the diagnosis of HES include eosinophil count of greater than 1.5x109/L, which persists beyond 6 months, and evidence of end-organ damage. Underlying causes such as parasitosis, allergy and drug reactions must be excluded. The PDGFR-α mutation is reportedly found in 17-56 % of cases of HES and was negative in both cases presented in this report. Imatinib therapy is recommended for patients with the PDGFR-α mutations who are usually steroid resistant.

Conclusion: HES is a rare disorder with serious potential for multi-system pathology. The accurate identification of the variant facilitates targeted therapy where this is applicable. The

favorable outcome in the reported cases is likely related to the absence of neurologic and cardio-pulmonary involvement.

Key words: Hypereosinophilic syndrome; Multisystem pathology; Imatinib

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INTRODUCTION

Hypereosinophilic syndrome (HES) is very rare with a prevalence of 1 to 2 per million people in the United States of America[1]. It is a heterogeneous group of disorders characterized by persistent eosinophilia with organ-system dysfunction related either to infiltration of eosinophils or eosinophil-associated tissue damage[2]. The three recently defined subtypes of HES are myeloproliferative, lymphocytic, and idiopathic variants[3].

We describe the cases of two female patients with HES who were treated successfully with oral steroids.

CASE REPORT

Case 1:

This female patient presented to our institution at 27 months of age with a 6-month history of progressive generalised abdominal pain, exacerbated by meals and relieved with simple analgesia. There was associated pica for dirt and a one year history of intermittent pruritic rash involving the eyelids. On clinical examination she was noted to have shotty cervical adenopathy, papular rash to the lower limbs and hepatosplenomegaly which was confirmed on abdominal ultrasound. Haematological evaluation revealed moderate normochromic, normocytic anaemia and leucocytosis with eosinophilia as outlined in Table 1. Histological examination of the skin biopsy shows marked superficial and deep perivascular inflammatory infiltrate composed mainly of eosinophils. An echocardiogram was normal. Based on the eosinophilia on the peripheral blood smear and the skin biopsy with negative stool cultures for parasites, the clinical diagnosis of hypereosinophilic syndrome was made. Immunoglobulin analysis revealed IgG 12, 300 mg/dl (normal range 800-1700 mg/dl), IgA 79.7 mg/dl (normal range 85-450 mg/dl), and IgM 223 mg/dl (normal range 60-370 mg/dl). The mutation analysis for PDGFR-α was negative (performed at Quest Diagnostics Incorporated, October 28, 2009). She was treated with prednisone 1mg/kg/day with a gradual decline in the eosinophil count reaching a nadir of 0.38 x 109/L with absent

hepatosplenomegaly in 2.5 months post therapy. Currently she is maintained on prednisone (dose range from 5 to 7.5 mg) daily and has developed hypertension controlled with hydrallazine.

Table 1: Results For Case 1

Time relating to starting treatment	Haemoglobin (g/dL)	Platelet Count (x109/L)	WBC (x109/L)	Absolute eosinophilic count (x109/L)
At presentation	7.0	518	40.30	27.00
1 month	9.5	579	19.20	4.22
3 months	9.7	441	12.40	3.45
6 months	11.4	282	7.96	0.59
1 year	12.3	363	10.50	0.84
1.5 year	14.0	362	15.10	4.29
2 years	13.4	442	10.60	1.2
2.5 years	13.3	341	12.40	1.3
3 years	13.9	305	8.40	5.4
4 years	14.3	330	12.5	1.89
5 years	13.9	377	9.67	0.946

Case 2:

A 30-year-old female with childhood history of mild intermittent asthma and a past history of a pituitary adenoma presented with a 2-month history of intermittent fever with malaise, dry cough and recent onset vomiting. There was no history of weight loss, anorexia, altered stool pattern, skin rash, myalgia or arthralgia. Hepatosplenomegaly was identified on physical examination and confirmed on abdominal ultrasound with associated fatty infiltration of the liver. Laboratory investigations as outlined in Table 2 revealed leucocytosis with eosinophilia and elevated LDH (1153 IU/L) with negative stool cultures for parasites. An echocardiogram was not performed. Based on the peripheral blood eosinophilia and the clinical findings she was diagnosed as likely hypereosinophilic syndrome. The PDGFR-α mutation analysis for exon 12 and 18 was negative (analysis performed at Quest Diagnostics Incorporated, May 12, 2011). She was commenced on prednisone at 1mg/kg/day and achieved a nadir of 0.41 x 109/L eosinophil count in 3 weeks with associated resolution of hepatosplenomegaly within 2 months. Therapy was then tapered to a maintenance dose of 7.5 mg daily. After developing the adverse effects of corticosteroids (steroid-induced diabetes mellitus and acne) she was offered alternative therapy but has refused.

Table 2: results for case 2

Time related to starting treatment	Haemoglobin (g/dL)	Platelet count (x109/L)	WBC (x109/L)	Absolute eosinophilic count (x109/L)
At Presentation	11.0	257	68.5	48.60
3 weeks	13.6	299	20.5	0.41
3 months	13.5	316	27.5	1.20
7 months	10.9	464	28.3	0.57
15 months	12.7	452	18.6	0.013

DISCUSSION

Hypereosinophilic syndrome was first described in 1968 by Hardy and Anderson[4]. There is variable reported incidence of the disorder from 1-2 per million to 5-10 per million[5]. The disorder reportedly has a higher incidence in whites and in males[6].

The pathophysiology of HES is based on endothelial damage with subsequent fibrosis, leading to infarction and thrombosis as a result of the release of eosinophil derived toxins from cells sequestered in organ systems. These include eosinophil-derived neurotoxin, eosinophil cationic protein and major basic protein. While any organ system may be involved, the burden of morbidity is due to dermatologic, neurologic and cardiopulmonary involvement. Serious illness or death usually related to endomyocardial fibrosis, myocardial infarction, restrictive cardiomyopathy or right heart failure. Pulmonary involvement usually presents with symptoms such as nocturnal cough and wheezing which may lead to a clinical diagnosis of asthma[7]. However in contrast to bronchial asthma there is no demonstrable air-flow limitation on pulmonary function tests. Nevertheless sporadic asthma may accompany HES. This situation seemingly existed in Case 2 in whom no pulmonary function tests were done, though she had a childhood history of wheezing. Neurologic involvement may produce a wide variety of neuropsychiatric symptoms reflected in aberrations of intellect, mood or co-ordination[8]. None of the cases reported displayed neurologic symptoms.

Criteria for the diagnosis of HES include eosinophil count of greater than 1.5x109/L, which persists beyond 6 months, and evidence of end-organ damage[2]. Underlying causes such as parasitosis, allergy and drug-related aetiology must be excluded. Additional features include organomegaly, polyclonal hypergammaglobulinemia and anemia. The discovery of the associated PDGFR-α mutation has been beneficial for further clarification of the pathogenesis, classification of the disease and selection of appropriate therapy.

Roufosse et al. (2003) noted the wide clinical heterogeneity of HES with the propensity for transformation to either myeloid or lymphoid malignancy[3].

This was assumed to suggest pathogenetic diversity with implications for therapy. The myeloproliferative variant of HES is characterized by an interstitial deletion of 4 q12 that results in fusion of FIP1L1-PDGFR-α genes; the fusion gene encodes a protein with tyrosine kinase activity. The importance of this mutation in the pathogenesis of this variant is underscored by the clinical and molecular response to imatinib therapy. The fusion gene also indicates disease with poor prognosis and a high risk of cardiac complications, as well as increased risk of AML. Pediatric cases of HES are usually negative for FIP1L1-PDGFR fusion[9].

In the two cases presented there was no objective evidence of either cardiopulmonary or neurologic pathology, though these are the most frequent and significant sites of organ involvement. An alternate diagnosis of Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss syndrome) could be considered in Case 2. However new onset asthma is a prominent feature of this disorder, while the patient had a history of childhood asthma that was no longer active. Additionally, the absence of granulomata, neuropathy and vasculitis

makes HES more likely[10]. The PDGFR-α mutation is reportedly found in 17-56 % of cases of HES and was negative in both cases presented in this report[11]. Imatinib therapy is recommended for patients with the PDGFR-α mutations who are usually steroid resistant. Both cases in this report showed prompt response to steroid therapy.

The lymphocytic variant of HES represents a lymphoid disorder in which an expanded T-cell population elaborates eosinophilopoetic cytokines such as IL-5. IL-5 producing T-cell subsets have been demonstrated in several patients with HES[12]. Other features of this variant include absence of male predilection, a history of atopic disease, pulmonary and gastro-intestinal end organ damage, and skin manifestations. A minority of patients manifest endomyocardial fibrosis even in the presence of high eosinophil counts. Some reports have underlined the comparatively low prevalence of end-organ damage in general and cardiac involvement in particular, which suggests superior short term prognosis[13,14]. Long term prognosis may be less favourable due to risk of T-cell neoplasms. Dermatologic abnormalities are widely variable and include pruritic lesions of macular papular or nodular morphology.

Roufosse et al. (2004) have recommended the use of imatinib or hydroxyurea for the myeloproliferative form of HES while the lymphocytic variant should be treated with cortico-steroids to which it is usually responsive[15]. Based on the clinical profile, absence of PDGFR-α mutation and responsiveness to corticosteroids, it is likely that the two cases presented represent the lymphoid variant of HES.

CONCLUSION

HES is a rare disorder with serious potential for multi-system pathology. The optimal clinical outcome depends on accurate identification of the variant, which facilitates targeted therapy where this is applicable. Early therapy to prevent end-organ damage is also advantageous.

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