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CASE SERIES

HYPER EOSINOPHILIC SYNDROME; A CASE SERIES

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ABSTRACT

Hyper eosinophilic syndrome (HES) is a subset of idiopathic eosinophilia that fulfils the criteria of a persistent (>6 months) increase in absolute eosinophil count (AEC) (>1.5×10⁹\l) associated with target organ damage. Recently it was classified into myeloproliferative and lymphoid variants. Present study is aimed to study the clinico morphological features and variants of HES and their response to various therapeutic modalities. In Pakistani population. It is a case series conducted at Haematology department, Shaikh Zayed hospital, Lahore during 4 years from Jan 2005 to Dec 2008. This study included 8 adult patients of HES diagnosed on history, clinical features and elevated absolute eosinophil count (AEC). Seven of 8 patients were of lymphoid-HES and 1 was of myeloproliferative-HES. M: F ratio is 7:1, mean age of presentation was 37 years in lymphoid-HES and 69 years in myeloproliferative –HES. Presenting features were fatigue, weight loss, fever, SOB, paraesthesia and skin rash. Mean AEC in l-HES was 16×10⁹/l and in myeloproliferative-HES was 22.7x10⁹/l. Organ damage was seen in cardiovascular, gastrointestinal (GIT), respiratory and nervous systems. All of the lymphoid-HES responded to steroids. In conclusion, early diagnosis and targeted therapy improve outcome in HES.

***Key Words**: Hypereosinophilic syndrome, HES, absolute eosinophil count.*

INTRODUCTION

Hypereosinophilic Syndrome is a group of disorders marked by the sustained over production of eosinophils (for > 6 months), in which eosinophilic infiltration and mediator release causes damage to multiple organs[1]. HES has substantial clinical heterogeneity but can be fatal without treatment.[2]

Due to the rarity of this disorder, clinical studies of the treatment of HES usually includes only a few patients. The literature is particularly devoid of clinical reports studying variants of HES. Although certain clinical findings indicate a poor prognosis in the natural history of patients with HES, It is important to study the clinical variants to determine if they are prognostically important in the face of the modern therapy for this disease. Objectives of present study were to observe the clinicohaematological features and variants of HES and their response to various therapeutic modalities.

PATIENTS AND METHODS

Eight patients of adult age group (> 15 yrs) of both genders diagnosed as having hypereosinophilic syndrome, during a period of four years i.e; from Jan. 2005 – Dec. 2008 were included in the study. Patients presented either in haematology OPD or were referred to Haematology department, Shaikh Zayed medical complex. All patients had absolute eosinophil count (AEC) >1500/ul for more than 6 months and evidence of organ damage. Patients with other causes of eosinophilia were carefully excluded according to the findings in history, physical examination and investigations.

From all selected patients, presenting complaints in history, findings in physical examination were recorded. CBC was done on Sysmax Kx-21. Peripheral smear were stained by giemsa for manual AEC. Bone marrow biopsy was done in all cases. Cytogenetic analysis for Philadelphia chromosome was done in all cases, while molecular genetics for FIP1L1 mutation were not performed due to non-availability. Multiple organ involvement is an important diagnostic criteria of HES. It was diagnosed by noninvasive investigations e.g echocardiography, ECG, x-rays, nerve conduction studies and pulmonary function tests. Consultation with dermatologist was part of workup when skin was involved.

All selected data was entered into SPSS version 10.0 for analysis and results were entered as mean, median, standard deviation, frequencies and percentages.

RESULTS

Case series included total 8 patients. Males were 87.5%, and females were 12.5%. Male to female ratio

was 7 : 1. Different signs, symptoms and laboratory parameters are analysed.

Seven patients were of lymphoid-HES variant, one patient was of myeloproliferative-HES variant. Age ranged from 28 to 69 years. Peak incidence was seen in fourth decade. Most of l-HES cases were in 4^{th} and 5^{th} decade. The only case of m-HES was an elderly male (69 years).

Duration of eosinophilia was more than 6 months in all cases and ≥ 12 months in 6 of 8 cases. Most common symptoms were fatigue (62%) and weight loss (50%). These were followed by fever (37%), SOB (37%), cough (25%), skin rash (25%), diarrhea (12%) and paresthesias (12%). The patient with m-HES had hepatosplenomegaly.

Multiple organ involvement is an important diagnostic criterion of HES. In one case of m-HES, there was extensive lung and cardiac involvement. Among seven cases of l –HES, cardiac involvement was seen in 42.8%, and skin involvement in 28.7%. Nervous system and GIT were involved in14.2% each.

In m-HES the only patient was a male. On CBC, Hb was 11.5gm/dl, TLC 28×10^9/ul, AEC 24.7×10^9/ul and platelet count 840×10^9/ul .Peripheral blood blasts were 1%,while bone marrow had 3% blasts. Bone marrow also showed fibrosis and increased mast cells. Serum vitamin B_{12} level was elevated. Philadelphia (Ph^1) chromosome was negative.

Analysis of haematological parameters in l-HES showed that all patients had a subnormal Hb (mean Hb 10.4 g/dl) and a high TLC (mean TLC 27.7×10^9/ul). All patients had either a normal or elevated platelet count, none had thrombocytopaenia. Mean AEC was 16×10^9/ul with a SD of 11.1×10^9/ul. Immature forms of eosinophils were seen on the smear but no blasts were seen.

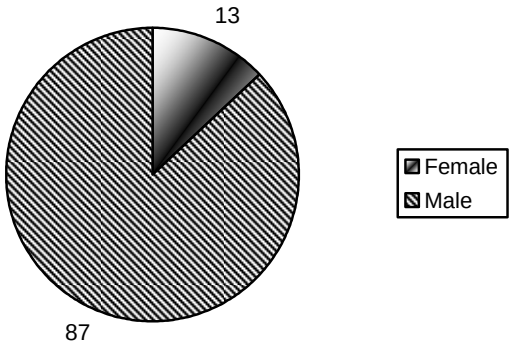

Fig. 1: *Gender distribution in eight cases of HES.*

In the present study response of patients to treatment was noticed. Response was defined as normalisation of AEC and decrease in disease related signs and symptoms. The patient of m-HES did not respond to steroids; however hydroxyurea was effective in reducing eosinophil count and splenomegaly. Imitanib was not used due to high cost. All patients of l-HES responded well to steroids.

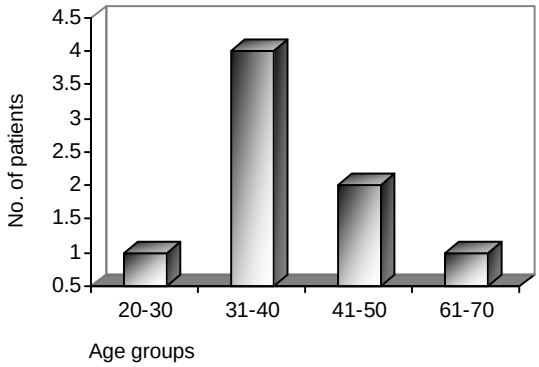

Fig. 2: *Age distribution in eight cases of HES.*

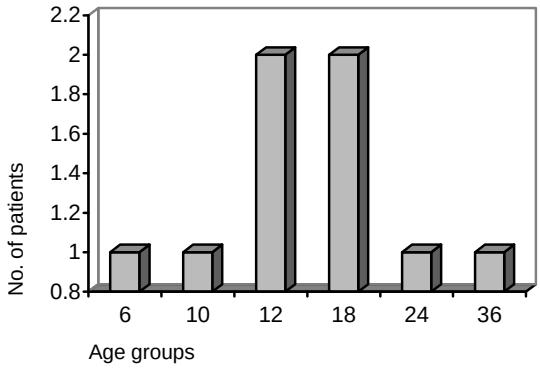

Fig. 3: *Duration of eosinophilia in eight cases of HES.*

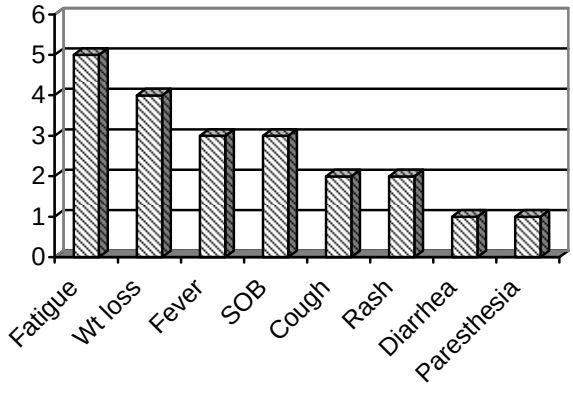

Fig. 4: *Signs and symptoms in eight cases of HES.*

DISCUSSION

Eosinophils are derived from myeloid progenitors (GEMM-CFU) in bone marrow, through the action

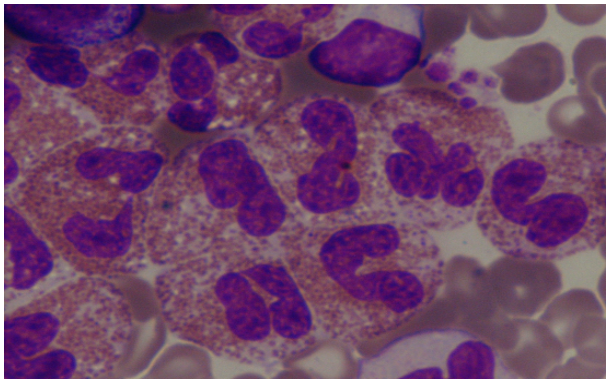

Fig. 5: *Bone marrow aspirate in HES (1000x).*

Table 1: *Organ involvement in eight cases of HES.*

Sr. No.	Organs involved	Lymphoid-HES (N = 7)	Myeloproli ferative-HES (N = 1)
1.	Heart	42.8%	100%
2.	Skin	28.7%	
3.	Nervous system	14.2%	
4.	GIT	14.2%	
5.	Lung		100%

Table 2: *Haematologic parameters in seven cases of lymphoid-HES.*

	Hb (g/dl)	TLC ($x10^9$/l)	Plts ($x10^9$/l)	AEC ($x10^9$/l)
Mean	10.4	27.7	411.6	16.0
Standard Deviation	2.2	12.2	308.6	11.1
Minimum	5.2	14.5	169	7.0
Maximum	12.3	54.0	1110	37.8

of three haematopoietical cytokines, GM-CSF, interleukin (IL) -3, and IL-5, among which only the latter is specific for eosinophil differentiation. Mature eosinophils are released into the blood stream and rapidly migrate to peripheral tissues, namely gut and bronchial mucosae and skin, where survival is short unless apoptosis is prevented by factors such as IL-3, IL-5, and/or GM-CSF.[3]

Hardy and Anderson first introduced the term HES in 1968[4]. In 1975, Chusid et al established the empirical diagnostic criteria of idiopathic HES (IHES) that are still in use today:

1. Persistent eosinophilia of over 1500/ul for longer than 6 months.
2. Lack of evidence of other known causes of secondary hypereosinophilia (SH).
3. Multiple organ involvement.[5]

Published patient series based on Chusid's diagnostic criteria have consistently shown that major tissue targets in HES include the skin, heart, and nervous system, with more than 50% of patients presenting with clinical complications in each of these sites.[6,7]

Chusid's original article, and all series that have followed, clearly illustrate the great clinical heterogeneity and highly variable prognosis of idiopathic HES, ranging paucisymptomatic disease requiring no treatment and associated with prolonged survival, to rapidly fatal disease course due to the sudden development of congestive heart failure or to the occurrence of acute leukemic disease[8].

Studies on the pathogenesis of HES have also revealed that the syndrome previously coined "idiopathic HES" comprised of pathogenetically distinct subtypes which are defined by molecular, immunephenotypic or clinical markers. Eosinophilia in HES can be caused by increased production or survival of eosinophils due to cytokines such as interleukin-5 or clonal expansion due to mutations[9].

The striking clinical heterogeneity among patients with idiopathic HES and the occasional development of malignancy involving either the myeloid or the lymphoid lineage was also noted by Roufosse et al. This finding strongly suggests pathogenic diversity. Recent observations indicate that distinct primitive haematological disorders involving either myeloid or lymphoid cells account for hypereosinophilia in patients fulfilling the initial diagnostic criteria of IHES.[8] Distinction of these pathogenetically different subtypes of HES is clinically relevant as new targeted treatment approaches are available for some of these subtypes.[9]

The myeloproliferative variant (m-HES)

A recent study has provided firm cytogenetic evidence for the existence of a clonal cytogenetic abnormality on detailed analysis of chromosome 4 in a subset of HES patients. An interstitial deletion on 4q12 resulting in fusion of FIP1L1 and PDGFRα genes was detected, and was then shown to be present in a further eight of 15 (53.3%) Idiopathic HES patients with apparently normal chromosome 4 according to routine karyotypes. The fusion gene is inframe and encodes a FIP1LI-PDGFR□ (F/P) protein displaying constitutive tyrosine kinase activity.[10] The central role of this fusion gene in disease patho-

genesis is supported by its disappearance in most patients successfully treated with imatinib.[11,12]

Other clinical and biological features frequently encountered in m-HES of interest to clinicians include anaemia and/or thrombocytopaenia, increased serum B12 levels, mucosal ulcerations, endomyocardial fibrosis, and splenomegaly.[10]

In a recent paper, Klion et al.[12] considered that diagnosis of m-HES was appropriate when four of eight laboratory criteria were fulfilled (i.e. presence of dysplastic eosinophils, increased serum B_{12}, increased serum tryptase, anaemia/ thrombocytopaenia, increased bone marrow cellularity with left shift, myelofibrosis, and dysplastic mast cells or megakaryocytes in bone marrow.[12] Additionally, it is likely that patients responsive to imatinib in whom the F/P mutation is not disclosed also present m-HES.[8]

Presence of the F/P mutation is indicative of a subgroup of m-HES patients with poor prognosis and a high prevalence of disease-related death due to development of cardiac complications and increased risk of developing AML. It can be hoped that timely administration of imatinib to these patients will modify the disease course and delay or prevent malignant transformation.[8] In the present study there was one male patient of m-HES. He presented with anaemia, increased serum B_{12}, increased marrow cellularity, marrow fibrosis and splenomegaly. He fulfilled the required (four of eight) laboratory criteria of m-HES. He had heart and lung involvement by the disease.

There are significant clinical differences between the pediatric and adult presentations of HES. No paediatric case with the FIP1L1-PDGFRA fusion gene has been reported to date[13].

The lymphocytic variant (l-HES)

The lymphocytic variant of HES (l-HES) can be defined as a primitive lymphoid disorder characterized by nonmalignant expansion of a T-cell population able to produce eosinophilopoietic cytokines (generally IL-5)[8].

In 1994, investigation of circulating T-cells isolated from a patient with HES and high serum IgE and IgM levels revealed the existence of an underlying T-cell disorder characterized by clonal expansion of a T-cell population able to produce IL-5 and IL-4, and bearing a unique CD3-, CD4+ (CD2+TCR α/β-) surface phenotype.[14] Since then, IL-5-producing T-cell subsets have been described in blood of about 35 patients with HES[8]. In a recent study, these cells were also shown to produce tumor necrosis factor -α and GM-CSF.[15]

In contrast to m-HES, l-HES appears to affect females at least as much as males. Clinical and biological profile shows, cutaneous manifestations, including pruritus, eczema, erythroderma, urticaria, and angioedema, observed in virtually all patients reported in the literature[8]. A previous history of typical atopic disease is frequently encountered.In contrast to m-HES, very few patients with l-HES develop endomyocardial fibrosis despite high eosinophil levels. Complications of hypereosinophilia in this subgroup of patients more commonly occur in the lungs and the digestive system. Report have shown rarity of end-organ damage (in particular heart involvement)and good short-term prognosis compared to m-HES, but long-term prognosis may be less favorable than once thought due to occurrence of T-cell malignancy.[8]

In the present study there were seven case of l-HES. Peak incidence was in fourth decade like previous reports[8], but in contrast to these our study showed a male predominance in l-HES. Organs involved were bone marrow in 100%, heart in 42.8%, skin in 28.7%, nervous system in 14.2% and gastrointestinal tract in 14.2%.

In NIH series[7] (when a distinction was not made in myeloproliferative and lymphoid variants), haematological involvement was seen in all cases, cardiovascular in 54%, skin in 56%, neurological in 64%, pulmonary in 40%, splenomegaly in 45%, hepatomegaly in 35%, and ocular involvement in 18%. Considering both variants together in our series these findings are consistent with our results (see Table 2). The organ involvement was consistent with other previous reports[16].

Multisystem involvement is a common feature of the aggressive form of idiopathic HES` but most of the morbidity and the cause of death are usually related to cardiac involvement. The most dramatic changes noticed at autopsy in a reported case were massive thrombosis with marked reduction in the capacity of the sinus portion of each ventricle[17].

About 50% of the patients suffer from skin manifestations. Skin lesions usually pruritic may be either erythematous macules, papules and nodules or urticaria, angioedema and dermographism. Additional lesions may include hyperpigmented macules, ulcerated nodules and vesicles, scaling, serpiginous lesions, subcutaneous nodules and palpable purpura.[18] Rarely skin eruptions may be the only manifestation of otherwise asymptomatic patient of HES.[19]

Neuropathy is produced by eosinophil-released substances exerting a neurotoxic effect through direct altered vascular endothelial permeability and local mast cell histamine release.[20]

Marolda et al described a case with polyneuropathic-like symptoms and disorders of the gastrointestinal tract. Peripheral nervous system changes were seen with EMG and nerve conduction studies.[21] Leiferman and Gleich reported that recurrent

mucosal ulcerations are a variant presentation of the HES that appear to be markers for a mutation that characterizes a subgroup of patients with HES responsive to treatment with imatinib mesylate (i.e. m-HES).[22] Chaudhuri K et al reported a case who had seropositive erosive RA for 10 years before developing HES. Disease responded well to steroids and cyclosporine.[23]

In the present study when response of patients to treatment was observed, the patient with m-HES was not responsive to steroids but to hydroxyurea. All patients with l-HES were responsive to steroids. These results were in accordance with literature.

Historically, corticosteroids and cytotoxic agents have been the mainstays of therapy, with biological response modifiers such as interferon-alpha also effective in some patients. More recently, new agents directed at specific targets in the pathogenesis of HES have been developed. These include imatinib mesylate, a tyrosine kinase inhibitor, and more recently, mepolizumab, an anti-IL-5 monoclonal antibody. In a small case series these agents have been shown to produce haematological and clinical responses in patients with HES, although they may be effective in different subsets of patients. These targeted therapies have the potential to improve clinical outcomes and to further the understanding the pathophysiology of this difficult-to-treat condition.[2]

Roufosse et al recommend that myeloproliferative variant should be treated by Imitnib, hydroxyurea or interferon alpha. In the presence of signs of malignant transformation consider chemotherapy / bone marrow or stem cell transplantation. Lymphocytic variant should be treated with glucocorticoids. Interferon-alpha can be added to steroids. Anti-IL-5 mAb is a new therapeutic option, its role remains to be assessed.[8]

It is **concluded** from the present study that HES although a rare disorder is a cause of considerable individual suffering and morbidity. Early diagnosis (before organ damage), identification of disease variant, specific targeted therapy and follow-up are required to improve the clinical outcome.

REFERENCES

1. Vassiliou G, Green AR. Myeloproliferative Disorders. In: Hoffbrand AV, Catovasky D, Tuddenham EG, editors. Postgraduate haematology. 5th ed. Oxford: Blackwell Publishing; 2005: 779.
2. Wilkins H. Jeffrey, Martin M. Crane, Kelly Copeland, William V. Williams Hypereosinophilic syndrome: An update, Am. J. Hematol 2005; 80: 148-157.
3. Wardlaw AJ. Eosinophils in the 1990s: new perspectives on their role in health and disease. Postgrad Med J. 1994; 70: 536–552.
4. Hardy WR, Anderson RE. The hypereosinophilic synd-romes. Ann Intern Med 1968; 68: 1220–1229.
5. Chusid MJ, Dale DC, West BC,Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature.Medicine (Baltimore) 1975; 54: 1–27.
6. Weller PF, Bubly GJ. The Idiopathic hypereosinophilic syndrome.Blood 1994; 83: 2759–2779.
7. Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med. 1982 Jul; 97 (1): 78-92.
8. Roufosse F, Cogan E, Goldman M. Recent advances in pathogenesis and management of hypereosinophilic syndromes Allergy 2004; 59: 673–689.
9. Hellmich B, Holl-Ulrich K, Gross WL. Hypereosinophilic syndrome--recent developments in diagnosis and treatment Dtsch Med Wochenschr. 2007 Sep; 132 (37): 1892-1896.
10. Klion AD, Noel P, Akin C, Law MA,Gilliland DG, Colls J et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. Blood 2003; 101: 4660–4666.
11. Pardanani A, Ketterling RP, Brockman SR, Flynn HC, Paternoster SF, Shearer BM et al. CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib therapy. Blood 2003; 102: 3093–3096.
12. Klion AD, Robyn JA, Akin C, Noel P, Brown MR, Law MA et al. Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. Blood 2004; 103: 473–478.
13. Katz H T, Jaharulhaque S, Hsieh F H. Pediatric Hypereosinophilic Syndrome (HES)differs from adult HES. J Pediatr 2005; 146: 134-136.
14. Cogan E, Schandene L, Crusiaux A, Cochaux P, Velu T, Goldman M. Brief report: clonal proliferation of type 2 helper T cells in a man with the hypereosinophilic syndrome. N Engl J Med 1994; 330: 535–538.
15. Roumier AS, Grardel N, Lai JL, Becqueriaux I, Ghomari K, de Lavareille A et al. Hypereosinophilia with abnormal T cells, trisomy 7 and elevated TARC serum level. Haematologica 2003; 88: ECR 24.
16. Sokol R.J, Hudson G, Brown M.J, Wales J, James N.T, Hypereosinophilic Syndrome: Case Report and Morphometric Study Acta Haematol 1988; 79: 107-111.
17. Hall SW, A Theologides, AH From, FL Gobel, IE Fortuny, CJ Lawrence and JE Edwards Hypereosinophilic syndrome with biventricular involvement Circulation 1977; 55: 217-222.
18. Desai D, Malkani R, Aswani V. The Hypereosinophilic Syndrome. Indian J Dermatol Venereol Leprol 2000; 66: 306-7.
19. Khare KC, Joshi P, Bhavsar R. Hypereosinophilic syndrome. Indian J Dermatol Venereol Leprol 2002; 68: 298-300.

20. Lupo I, Daniele. O, Raimondo D, Rodolico V, Camarda R.M Peripheral Neuropathy in the Hypereosinophilic Syndrome: A Case Report. Eur Neurol 1989; 29: 269-272.
21. Marolda M, Orefice G, Barbieri F, Striano S, Campореale F.S, Santagelo R, Vecchione V, Catalano A, Crisci C and Ragno M. The idiopathic hypereosinophilic syndrome. Clinical, electrophysiological and histological study of a case The Italian Journal of Neurological Sciences 1989 FEB; 10 (1): 79-84.
22. Leiferman KM, Gleich GJ Hypereosinophilic syndrome: case presentation and update. J Allergy Clin Immunol. 2004 Jan; 113 (1): 50-58.
23. Chaudhuri K. Dubey S, Zaphiropolous G. Idiopathic hypereosinophilic syndrome in a patient with longstanding RA, a case report. Rheumatology 2002; 41: 349-350.