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Review Article

Management of hypereosinophilia in tropical settings

Arjun Datt Law^a, Subhash Chander Varma^{b,*}

^a Senior Resident & Clinical Haematologist, Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

^b Professor & Head, Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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ABSTRACT

Hypereosinophilia includes a group of commonly encountered clinical situations with symptoms ranging from mild and clinically innocuous to devastating presentations with high morbidity and mortality. The presentations and complications can be easily missed if the clinician is unaware of the diverse entities responsible for hypereosinophilia. The hypereosinophilic syndromes encompass entities that are associated with varying degrees of organ dysfunction either directly due to eosinophilic infiltration or as a result of substances secreted by the eosinophils. These conditions may be neoplastic or reactive in aetiology and a diligent search for secondary causes is essential. Evaluation and management algorithms in the tropical setting and in developing countries may differ from elsewhere. A review of hypereosinophilia and hypereosinophilic syndromes is presented with a diagnostic and therapeutic decision making algorithm modified for use in the tropical setting.

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Introduction

Eosinophils are integral components of the immune system that are derived from myeloid progenitor cells. So named due to their typical staining characteristics with Romanowsky stains, eosinophils are increasingly being recognised as key modulators of local and systemic inflammatory processes. Hypereosinophilia refers to an absolute increase in eosinophils with or without associated tissue infiltration. The term hypereosinophilic syndrome refers to a heterogeneous group of disorders characterised by the marked overproduction of eosinophils and tissue or organ dysfunction resulting from the

same. The increased number of eosinophils may incite organ damage by direct infiltration of tissues or by the release of mediators contained within intracellular granules. A variety of clinical manifestations have been associated with hypereosinophilia, ranging from innocuous and relatively minor to catastrophic and life threatening. The etiological factors associated with the development of hypereosinophilia also range from reactive causes associated with tropical infections (especially helminths) to haematological malignancies. The spectrum of eosinophilia seen in tropical regions and developing countries may have a higher percentage of infection or parasitic infestation related reactive hypereosinophilia.¹

* Corresponding author. Tel.: +91 9914209671 (mobile).

E-mail address: suvarma@hotmail.com (S.C. Varma).

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Pathophysiology

Eosinophils are key mediators of local and systemic inflammation especially that associated with parasitic organisms and allergic or atopic disorders. The eosinophil is a highly granulated cell containing a plethora of inflammatory cytokines, chemotactic agents, enzymes and growth factors. Under a variety of stimuli, degranulation and release of these granule contents results in alteration of tissue structure, integrity and homeostatic mechanisms. Interleukin-5 (IL-5) plays a key role in the survival and proliferation of eosinophils and has been used as a therapeutic target in hypereosinophilic syndromes for the anti-IL-5 monoclonal antibody mepolizumab.² Other key growth and differentiation factors involved in eosinophilopoiesis are GM-CSF and interleukin-3 (IL-3).³

The organ and tissue damage associated with hypereosinophilia may be related to release of eosinophil granule contents as well as secondary to direct infiltration of these tissues by eosinophils. Indeed, the presence of eosinophil granule proteins in tissues forms part of the defining criteria for hypereosinophilia.⁴ Many typical and characteristic manifestations of hypereosinophilic syndromes occur as a result of these pathogenic mechanisms. Inflammatory changes and subsequent fibrosis is a frequently encountered scenario and may result in lasting sequelae, especially when affecting the cardiovascular system. The role of profibrotic agents such as TGF- β 1 has also been studied in eosinophilic disorders such as eosinophilic oesophagitis.⁵

Thrombotic complications are an important aspect of the hypereosinophilic syndromes and may present with severe and multifocal thrombotic events affecting both arterial and venous circulations.⁶ Eosinophil granule contents are frequently implicated in the pathogenesis of thrombosis in HES. Eosinophil Cationic Protein (ECP) has been reported to bind endogenous heparanoids and enhance factor XII activity. ECP may also bind to thrombomodulin leading to impairment of its anticoagulant activity and increased thrombogenesis.⁷ Eosinophils also contain tissue factor which upon release during eosinophil degranulation, leads to activation of the coagulation pathway. Other eosinophilic contents such as the Major Basic Protein (MBP), arachidonic acid metabolites, eosinophil peroxidase and reactive oxygen species are also implicated in thrombogenesis by their direct action on vascular endothelium and platelet pro-aggregant properties.⁸

These mechanisms may result in significant organ impairment and may lead to life threatening end organ damage.

Causes of hypereosinophilia and classification of HES

The diagnostic criteria for the diagnosis and classification of hypereosinophilia were first described by Chusid et al in 1975.⁹ A recent consensus on terminology defined hypereosinophilia (HE) as eosinophilia $>1.5 \times 10^9/L$ in the peripheral blood on two occasions >1 month apart with or without tissue hypereosinophilia. Hypereosinophilic syndrome (HES) is defined as peripheral blood hypereosinophilia with organ damage and/or dysfunction attributable to tissue HE and the exclusion

of other disorders or conditions as major reason for organ damage.⁴ Organ damage in the form of fibrosis, cutaneous manifestations, thrombotic complications and neuropathy in the presence of marked tissue infiltration was considered. Earlier definitions required the persistence of eosinophilia and organ dysfunction for six months prior to diagnosis. This criterion has since been removed keeping in mind that patients may develop rapidly progressive organ dysfunction necessitating early intervention and evaluation and exclusion of secondary causes may be carried out faster. The distinction between peripheral blood or bone marrow eosinophilia and tissue eosinophilia is important as eosinophilic disorders may not always be associated with tissue infiltration and vice versa. Organ restricted hypereosinophilic disorders have also been described and are associated with eosinophilic infiltration into specific tissues with or without peripheral blood HE (Table 1).

Hypereosinophilia has been separated into the distinct entities of primary clonal or neoplastic HE (HE_N) wherein the eosinophilia is as a result of neoplastic eosinophils, hereditary or familial HE (HE_{FA}), secondary or reactive HE (HE_R) and HE of undetermined significance (HE_{US}).⁴ HE_N and HE_R represent an etiopathological classification of the HE at the point of initial evaluation and do not necessarily indicate the final diagnosis. They may be considered as intermediate points enabling appropriate decision making regarding further diagnostic evaluation. The entity HE_{US} encompasses a subset of patients that have persistent eosinophilia for which a clear aetiology cannot be identified. The prognosis of this subgroup remains uncertain and warrants careful and long term monitoring. Importantly, these patients may remain asymptomatic for varying periods. An individualised form of monitoring directed towards evaluation of organ dysfunction in addition to eosinophilia may be prudent in these patients.

HE_N includes entities defined by the WHO classifications as Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of platelet-derived growth factor receptor alpha (PDGFRA), platelet derived growth factor receptor beta (PDGFRB), or fibroblast growth factor receptor 1 (FGFR1) and Chronic Eosinophilic Leukemia – Not otherwise Specified.¹⁰

HE_R is likely to include the majority of cases encountered in tropical and developing countries. This entity comprises of cases where the eosinophilia is not clonal or neoplastic but usually occurs secondary to cytokines (such as IL-5) released by another inciting event. Common causes include allergic/atopic disorders, helminthic infections, drug allergies, infestations, autoimmune diseases, allergic bronchopulmonary aspergillosis or rarely, underlying solid tumours or hematolymphoid malignancies such as Hodgkin lymphoma, Langerhans cell histiocytosis and acute myeloblastic and lymphoblastic leukemias. Important causes that must be considered in tropical settings include tuberculosis and HIV. Hypereosinophilia may be seen in pulmonary and extrapulmonary tuberculosis as well as disseminated forms, where it may be associated with adrenal insufficiency. HIV associated HE may be due to the virus itself or as a result of opportunistic infections.

Hypereosinophilic syndromes (HES) have also been separated into subcategories depending upon their aetiology. These include primary neoplastic HES_N, secondary or reactive HES_R and idiopathic HES.

Table 1 – Causes of hypereosinophilia.^a

Allergic disorders, eg.
Allergic bronchopulmonary aspergillosis (ABPA)
Atopy and related disorders
Drugs, eg.
Allopurinol
Carbamazepine
Phenytoin
L-Tryptophan
Dermatological disorders, eg.
Allergic contact dermatitis
Bullous pemphigoid
Eosinophilic vasculitis
Incontinentia pigmenti
Kimura disease
Pemphigus
Urticaria
Haematological disorders, eg.
Acute leukemias with eosinophilia
Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
Acute and chronic eosinophilic leukemia
Myelodysplastic syndromes or myeloproliferative neoplasms with eosinophilia
Hodgkin lymphoma
B and T cell non Hodgkin lymphomas
Systemic mastocytosis
Langerhans cell histiocytosis
Immunological disorders, eg.
Vasculitis (Eosinophilic granulomatosis with polyangiitis, ANCA associated vasculitis)
Gleich syndrome
Omenn syndrome
Hyper IgE syndrome
Eosinophilia myalgia syndrome
Graft rejection and Graft versus Host disease (chronic)
Infestations, eg.
Ascariasis
Filarial infections (<i>Wuchereria</i> , <i>Brugia</i> , <i>Mansonella</i> species)
Giardiasis
Hookworm Infection
Paragonimiasis
Trichinosis
Schistosomiasis
Scabies and other entomological infestations
Strongyloidiasis
Solid tumours
Specific organ limited eosinophilic syndromes, eg.
Eosinophilic gastritis
Eosinophilic colitis
Eosinophilic pneumonia
Eosinophilic cystitis
Eosinophilic fasciitis
Eosinophilic panniculitis

^a List is representative of commonly encountered conditions, more comprehensive resources may be found online.

Approach to diagnosis

The clinical manifestations and presentations of HE and HES are as varied and heterogeneous as their etiologies. Patients may present with features directly attributable to the hyper-eosinophilic state or with features of the underlying disorder. A diagnostic/therapeutic algorithm such as the one depicted

in Fig. 1 may be appropriate in tropical or developing countries.

A comprehensive diagnostic panel for HES (Table 2) should include a complete blood count with differential count. Morphology of the eosinophils can sometimes provide clues regarding aetiology.¹¹ Evaluation of metabolic parameters including renal and liver function tests can give information about possible tissue infiltration and organ dysfunction. Further evaluation should be directed towards two goals, to identify the cause of HE and to identify the organs or tissues affected by the same and to what degree. Care should be taken to identify the most likely causes in a given setting, for instance to search for evidence of helminthiasis or other parasitic infestations, in a patient presenting from a rural background in a developing or tropical country. A therapeutic trial of antihelminthics may be prudent at first contact in areas where intestinal helminthiasis is likely to be the most common factor. Failure to respond should prompt investigation into other likely causes. At our centre, a 21 day course of the microfilaricide Diethylcarbamazine (DEC) is often used in patients who do not respond to antihelminthics such as albendazole or mebendazole leading to good responses (unpublished data). Mantoux testing, chest radiography and sputum examinations should be done in patients likely to have tubercular infection. HIV serological examination is prudent in high risk populations.

Stool examination for ova or cysts of parasitic helminths should be undertaken in all cases. Screening of the peripheral blood for microfilaria should be done in patients from endemic areas such as parts of the Indian subcontinent. Consumption of raw freshwater molluscs in parts of South East Asia may result in Paragonimiasis. Serum IgE levels may be elevated in allergic conditions. A carefully elicited history and thorough physical examination can provide vital clues to the diagnosis. A history of travel from a helminthiasis affected area or exposure to drugs or chemicals are important points that should be looked for. The presence of splenomegaly on physical examination may indicate the presence of a myeloproliferative neoplasm. Lymphadenopathy with or without hepatosplenomegaly may suggest a lymphoproliferative disorder. Respiratory findings may indicate either a pre-existing airway disease such as allergic bronchopulmonary aspergillosis or be a manifestation of organ dysfunction caused by the HE itself. Pulmonary function testing, imaging of the chest and bronchoscopic evaluation may provide corroborative evidence. Systemic vasculitides such as associated with HES and presentations may vary according to tissues and structures affected. Serological examination for connective tissue disorders and autoimmune conditions should be carried out in these patients. Cutaneous manifestations are common but diverse and care must be taken to identify lesions prior to the onset of therapy. A cutaneous biopsy is often recommended to confirm the diagnosis on histopathology and immunofluorescence. Tissue sampling from other affected areas is also highly informative and should be attempted wherever possible. Imaging of the chest and abdomen by computerised tomography may give additional information particularly in patients with respiratory findings or where vasculitis is suspected. Assessment of cardiac function by echocardiography or cardiac magnetic

Fig. 1 – Diagnostic and therapeutic approach to hypereosinophilia and the hypereosinophilic syndrome in tropical settings.

resonance imaging in addition to biomarkers such as cardiac troponin and n-terminal brain natriuretic peptide is important to identify early signs of valvular abnormalities, cardiac failure or endomyocardial fibrosis as well as evidence of intracardiac thrombi.¹²

In case a reactive cause of eosinophilia cannot be identified in the initial diagnostic battery, it is recommended to proceed with a bone marrow examination and other investigations to rule out clonal disorders. Immunophenotyping of peripheral blood and bone marrow is also recommended. Flowcytometry of the T-lymphocyte population can assist diagnosis of the lymphoproliferative variant of HES which is associated with the presence of a polyclonal but phenotypically abnormal subset of t-lymphocytes that may be CD3⁺CD4⁺CD8⁺, CD3⁺CD4⁺CD8⁺ or CD4⁺CD7⁺ although other subsets are reported.¹³ This variant may also be associated with elevated IL-5 levels. Serum thymus and activation-regulated chemokine

(TARC) levels may also be elevated in this variant.¹⁴ Clonality of the T-cells may be demonstrable through analysis of the T-cell receptor rearrangement pattern.

Overt acute myeloid and lymphoblastic leukemias may be associated with HE. Acute myeloid leukemia FAB variant M4 may be associated with HE and is designated as AML-M4Eo. The cytogenetic abnormality inv(16) (p13.1q22) or t(16; 16) (p13.1; q22); CBFB-MYH11 is associated with varying degrees of eosinophilia.¹⁵ Bone marrow eosinophilia may also be seen in AML with t(8; 21) (q22; q22); RUNX1-RUNX1T1.¹⁶ Acute lymphoblastic leukemias have also been associated with peripheral blood and marrow eosinophilia.¹⁷

Myeloproliferative disorders causing eosinophilia are diagnosed on the basis of characteristic bone marrow examination findings and the presence of causative genetic abnormalities such as the FIP1L1-PDGFR α , PDGFR β and FGFR1 rearrangements. The use of Fluorescent in-situ hybridization

Table 2 – Investigations useful in the evaluation of HE.

Complete Blood Count with differential leucocyte count ^a
Liver and kidney function Tests ^a
Stool microscopy ^a
Urinalysis ^a
Blood microscopy for microfilaria ^a
Serological tests for parasites ^a
Viral serologies
Antinuclear antibodies (ANA)
Anti-neutrophil cytoplasmic antibody (ANCA)
Serum tryptase level
Serum Vitamin B12 level
Cardiac enzymes and biomarkers (Troponin)
Histopathological examination of involved tissues
Endoscopy and biopsy if gastrointestinal manifestations are present
Radiology – Chest X-ray ^a , Computerised tomography of the chest, ultrasonography
Cardiac evaluation – Electrocardiography, echocardiography, cardiac magnetic resonance imaging
Pulmonary function testing
Bone marrow aspiration and trephine biopsy
Flowcytometry of peripheral blood or bone marrow aspirate
Molecular studies – FISH or PCR for Bcr/Abl, JAK2 ^{V617F} , FIP1L1/PDGFR α , PDGFR β and FGFR1 rearrangements
T-cell receptor rearrangement analysis
Conventional cytogenetics
IL-5, IL-3 and GM-CSF levels

^a Recommended in all cases at baseline.

(FISH) or Polymerase Chain Reaction (PCR) for the detection of these characteristic genetic abnormalities is increasingly available and enables rapid and accurate diagnosis. Serum vitamin B12 and tryptase levels are frequently elevated in patients with myeloproliferative disorders and HE.^{18,19} In the presence of other haematological features suggesting a myeloproliferative neoplasm (eg. massive splenomegaly, elevation of other cell lines) it may be prudent to test for the Bcr-Abl and JAK2^{V617F} transcripts by PCR or FISH as well. Systemic mastocytosis may be associated with HE and the KIT D816V1 mutation. Clonal eosinophilia in the absence of any distinctive cytogenetic or molecular abnormality may meet the diagnostic criteria for CEL-NOS.

The diagnosis of Idiopathic HES is one of exclusion and must be considered only after a thorough and diligent search.

Treatment considerations

The management of HES often hinges upon the underlying disease state and the severity of organ dysfunction. Often, management of the underlying disease state controls the hypereosinophilia effectively. In the case of HES associated with systemic vasculitis, immunosuppressive therapy like steroids and cyclophosphamide are effective in controlling both HE and its manifestations. Control of the inciting infective process or parasitic infestation effectively controls HE in the majority of cases of HE_R.

The use of the tyrosine kinase inhibitor Imatinib has changed the management of myeloproliferative neoplasms associated with the FIP1L1-PDGFR α rearrangement. Relatively lower doses (100 mg per day) have been shown to be effective

in this and other myeloid disorders with HE, to the point of showing dramatic reversal of end organ damage as well.²⁰ Long term responses may be possible with this well tolerated agent. Imatinib may have some utility even in patients that are FIP1L1-PDGFR α negative and a therapeutic trial may be warranted in steroid unresponsive cases. Other tyrosine kinase inhibitors such as nilotinib, sorafenib and ponatinib have also been evaluated for this indication but are in early clinical trials at present.²¹

The management of HES without imatinib sensitive mutations is focused upon rapid reduction of eosinophil counts and limitation of end organ damage. The mainstay of therapy in these cases is the use of corticosteroids. Initial high dose steroid therapy may be utilized to rapidly reduce eosinophil counts and be followed by a gradually tapering course of oral steroids, usually prednisolone at a dose of 1 mg/kg to begin with. Steroids may result in responses in up to 85% cases by one month however prolonged maintenance doses may be needed.²² Once a response is achieved, steroids can be tapered to the lowest effective dose. Other agents such as vincristine and cyclophosphamide may be used for acute lowering of eosinophil counts, the latter being particularly useful in HES associated with systemic vasculitis.^{23,24} For patients who do not respond adequately to corticosteroids, alternative medications include hydroxyurea and interferon.²⁵ Hydroxyurea is used initially in doses of 500 mg/day and can be increased to up to 2000 mg/day. Haematological and gastrointestinal adverse events including mucositis may be dose limiting. Teratogenicity is an important consideration. Interferon is a useful agent in steroid unresponsive HES by virtue of its immunomodulatory effects. Interferon alfa may be useful in doses from seven to fourteen million units per week. Pegylated forms may also be used. Flu-like syndrome, fatigue, thyroid dysfunction and depression are important adverse events. Doses may be reduced or the dose interval increased in stable patients. Therapy with cyclosporine has been shown to be effective in patients with the lymphoproliferative variant of HES.²⁶

Novel therapies

Mepolizumab is a humanised monoclonal antibody directed against IL-5. It has been used in the management of steroid refractory idiopathic HES with an acceptable safety profile and encouraging results as a steroid sparing agent and is particularly useful in the management of lymphocytic variant related HES.² Despite encouraging data, the clear role of mepolizumab remains to be defined. The use of this and other agents earlier in the course of disease may offer better responses as compared to use in patients with advanced and/or steroid dependent disease.

Reslizumab is another anti-IL-5 humanised monoclonal antibody developed for use in patients with eosinophilic oesophagitis and asthma.²⁷ Studies of its efficacy in HES are pending.

Alemtuzumab is another monoclonal antibody directed against CD52, which is expressed on eosinophils as well as T-lymphocytes. Small trials and case reports have demonstrated

the efficacy of alemtuzumab in idiopathic and lymphocytic variant HES however data is insufficient to warrant its routine use in this setting.²⁸ The risk of prolonged immunosuppression leading to cytomegalovirus reactivation is an important consideration.

Allogeneic haematopoietic stem cell transplantation with myeloablative and non-myeloablative conditioning has been attempted in refractory cases with varying degrees of success, with disease free survival rates of up to 5 years.²⁹ Transplantation may be considered for patients with refractory disease however its role is controversial.

Special considerations

Thrombotic complications are frequently seen in patients with HES. Although there is no well defined role of prophylactic anticoagulation in these patients, close monitoring and early initiation of anticoagulant therapy in patients at risk is warranted. Cardiac mural thrombi can result in systemic embolic phenomena and should be treated with anticoagulant therapy with warfarin. Catastrophic thrombosis affecting multiple sites including the arterial circulation has also been described.⁶

Cardiac dysfunction has been shown to be responsible for mortality in 33% of patients dying due to HES.³⁰ Manifestations can range from valvular disorders, eosinophilic myocarditis resulting in endomyocardial fibrosis and intracardiac thrombogenesis. Valve replacement with a bioprosthetic or mechanical valve, endomyocardectomy or thrombus removal may be performed as necessary.

Conclusion

Hypereosinophilia is a condition with myriad clinical manifestations and etiologies ranging from clinically innocuous presentations to devastating and rapidly fatal ones. A careful search into the causative mechanisms is required as the eosinophilia may be secondary to another underlying disease. In developing countries it is important to consider parasitic infestations as a cause of HE and empiric treatment with antihelminthic drugs or microfilaricides may produce gratifying outcomes. A structured diagnostic and therapeutic algorithm is useful to guide clinical decision making. Rapid initiation of therapy is essential in conditions where end organ damage has begun in order to limit morbidity and mortality.

Conflicts of interest

All authors have none to declare.

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