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Review Article

Management of hypereosinophilia in tropical settings

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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.

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, eosinphils 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]

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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-β1 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 peroxidise 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 × 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.