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HYPEREOSINOPHILIA: A GUIDELINE FOR WORKUP IN THE ALLERGY COMMUNITY

INTRODUCTION

Determining the etiology of eosinophilia, defined as an absolute eosinophil count (AEC) greater than 500 cells/μL, is often difficult given the many potential causes spanning several medical specialties. The diagnosis becomes more urgent in the case of hypereosinophilia (≥1,500 cells/μL)[1] due to concerns over potential end organ damage. The goal of this review is to educate physicians about the biology, etiologies, and workup of hypereosinophilia.

BIOLOGY

Eosinophils represent up to 6% of total bone marrow nucleated cells where cytokine-mediated growth and maturation is regulated by interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-5[2]. IL-5 is essential for eosinophil survival and mobilization from the marrow. Mature eosinophils are recruited to tissues where they mediate numerous immune responses through cytokine interactions with other immune response cells, including mast cells and T-lymphocytes[2].

Eosinophils also regulate immune responses and direct systemic reactions via intracellular primary and secondary granules. Primary granules contain a protein that forms Charcot Leyden crystals, regulate T-cells, and have lysophospholipase activity. Specific granules contain proteins, such as major basic protein, that are directly cytotoxic towards cells and regulate mast cell degranulation. These proteins can damage host tissue through infiltration, fibrosis, thrombosis, and allergic inflammation[3]. The most commonly damaged organ systems include gastrointestinal (eosinophilic gastrointestinal disorders), pulmonary (eosinophilic asthma/pneumonia), upper airways/sinuses (eosinophilic chronic rhinosinusitis), cardiac, and neurologic (hypereosinophilic syndromes) tissues[3].

CAUSES OF EOSINOPHILIA

Most cases of eosinophilia are benign[4,5] and can vary based on age or geography. In pediatric patients, secondary hypereosinophilia (≥1,500 cells/μL) from atopic dermatitis, graft-vs-host disease, sickle cell disease, and parasitic infections are most common[6]. In adults with mild eosinophilia (1,000 cells/μL), common causes include bacterial infections, asthma, chronic lymphocytic leukemia (CLL), and multiple myeloma (MM)[7]. Researchers have demonstrated that 86% of outpatient hematology patients presenting with eosinophilia had an allergic etiology including eosinophilic chronic rhinosinusitis (ECRS), eosinophilic granulomatosis and polyangiitis (EGPA), and severe asthma[5,8,9]. Beyond age differences, geographic location may also provide insight into the common causes of eosinophilia. Patients from tropical areas are at increased risk of developing eosinophilia through infection, highlighting the importance of obtaining a thorough travel history[10]. Common infectious causes for reactive eosinophilia include helminths (e.g., strongyloidiasis, trichinellosis, schistosomiasis), parasites (e.g., scabies), protozoans (e.g., isosporiasis), fungi (e.g., coccidiomycosis), and viruses (e.g., human immunodeficiency virus)[11].

WORKUP FOR EOSINOPHILIA

A vital step in the diagnosis, treatment, and management of hypereosinophilia involves determining the urgency of the patient's presenting symptoms. Hypereosinophilia (cell counts exceeding 50,000 cells/μL) often presents as severe illness requiring emergent hospitalization to expedite treatment[10]. Symptomatic but clinically stable patients warrant further investigation within days[10]. Asymptomatic patients or incidental eosinophilia requires follow-up depending on the AEC. Eosinophilia greater than 1,500 cells/μL, regardless of symptoms, should be reassessed within two weeks to ensure that the AEC is not increasing[10,12] (**Figure 1**). A thorough drug, travel, allergy, and medical history along with specific physical examination of all major organ systems is essential[10].

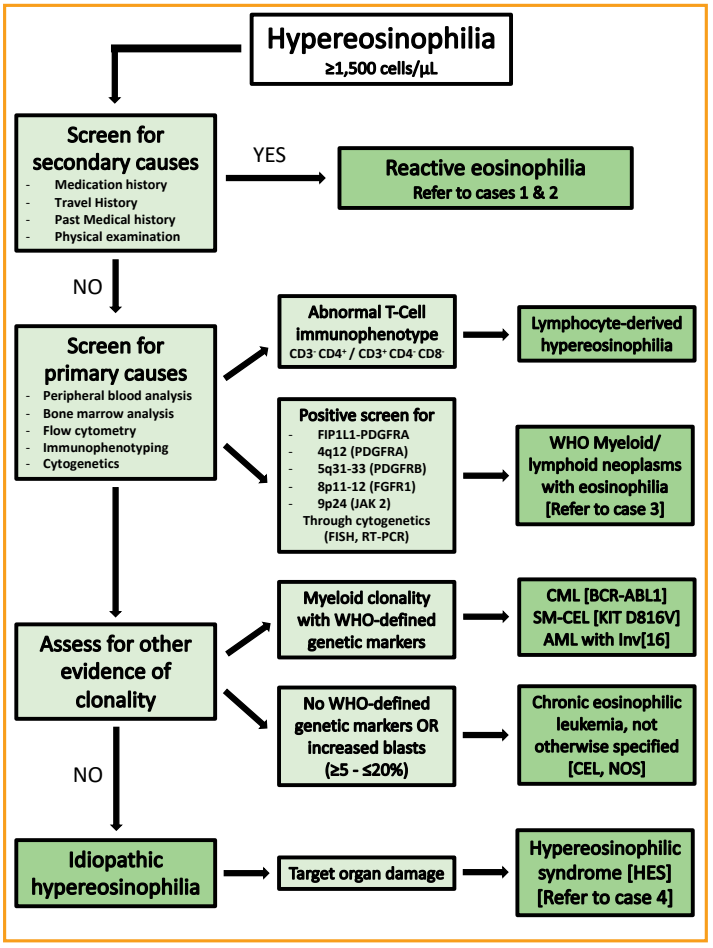

Figure 1.: FIP1L1 = Factor interacting with PAPOLA and CPSF1; PDGFRA = Platelet-derived growth factor receptor alpha; PDGFRB = Platelet-derived growth factor receptor beta; FGFR1 = Fibroblast growth factor receptor 1; JAK 2 = Janus kinase 2; FISH = Fluorescence in situ hybridization; RT-PCR = Reverse-transcription polychain reaction; CML = Chronic myeloid leukemia; SM-CEL = Systemic mastocytosis chronic eosinophilic leukemia; AML = Acute myeloid leukemia; courtesy of O'Connell and Sussman, 2022

Non-specialized tests such as complete blood count and differential, erythrocyte sedimentation rate, c-reactive protein, and proteinuria can provide diagnostic information to rule out benign causes of eosinophilia[4]. Specialized tests to assess for allergic causes include measuring IgE levels, specific antibodies to allergens (e.g., *Aspergillus*), or assessing for parasitic causes through serology and/or stool microscopy (i.e., antibodies or eggs)[4]. If there is no clear secondary cause for eosinophilia, referral to a specialist(s) should be considered (**Figure 1**).

CASES

Case 1: Infectious case of eosinophilia

A 48-year-old male (originally from Somalia; sheep farmer) presented with a cough, generalized abdominal pain, and fever (40.1°C) after returning from Somalia 9-months earlier. Initial imaging demonstrated bilateral lower lobe infiltrates, and CT imaging detected ill-defined hypodense liver lesions. The patient had elevated eosinophils (8,200 cells/µL) and normal transaminases. A liver biopsy identified necrotic areas and eosinophilic infiltrates suspicious for echinococcal abscess. Infectious disease experts felt further testing was warranted. Serological testing for *Strongyloides stercoralis, Entamoeba histolytica, Toxocara* species, and *Schistosoma* species were negative. Examination of a stool specimen detected *Blastocystis hominis* and *Fasciola hepatica* eggs. The patient was diagnosed with fascioliasis secondary to a liver fluke and was treated with triclabendazole; the liver lesions and eosinophilia resolved.

Comment: This case underscores the importance of a patient's travel history and the coordination of care with infectious disease experts. The original pathology suggested echinococcal disease whereas the consultant physician felt additional lab tests were needed, leading to the correct diagnosis and treatment. Clinicians should always consider parasitic and infectious causes of eosinophilia prior to initiating treatment. Glucocorticoids are appropriate first line treatment for reactive eosinophilia. If strongyloidiasis is suspected, concomitant steroid and ivermectin treatment is strongly recommended as steroids alone can lead to hyper-infection[13].

Case 2: Eosinophilic asthma resistant to chronic oral glucocorticoids

A 40-year-old man was diagnosed with eosinophilic asthma and was steroid-dependent. Treatment with mepolizumab during a clinical trial resulted in an excellent response, however at the end of the clinical trial, further anti-IL-5 antibody treatment could not be accessed for the patient. As a result, the patient's worsening asthma symptoms required resumption of oral prednisone (20 mg daily). The patient was subsequently enrolled in another clinical trial evaluating benralizumab, a humanized monoclonal antibody targeting the alpha subunit of the IL-5 receptor. The patient responded to benralizumab treatment and was able to reduce his prednisone dose to 2.5 mg daily.

Comment: A small subset of asthma patients have eosinophilic asthma. The pivotal role of IL-5 in eosinophil differentiation, survival, and migration makes this cytokine an ideal target for treatment. This treatment involving the targeting of the IL-5 pathway significantly reduces exacerbations of asthma, as well as blood and sputum eosinophils, even under reduced steroid usage[14,15]. Research has shown that mepolizumab is effective in reducing steroid dosing in patients with eosinophilic asthma.[5]

Case 3: Eosinophilia presenting as a clonal myeloproliferative disorder

A 58-year-old previously healthy male presented with drenching night sweats, headaches, and fatigue of two weeks duration. His AEC was markedly elevated (45,600 cells/µL) with hemoglobin and platelet counts mildly decreased. Lab tests revealed normal serum creatinine, transaminases, and total bilirubin counts, while troponin was elevated to 9995 ng/L. An echocardiogram showed multiple wall motion abnormalities and an MRI of the brain detected multiple areas of bilateral subacute ischemia in watershed distribution. Nerve conduction studies confirmed axonal motor polyneuropathy. Treatments with oral steroids and hydroxyurea were initiated. A bone marrow exam demonstrated increased eosinophilic precursors and the blast count was <5% (**Figure 2**). Cytogenetics confirmed a male karyotype and interphase fluorescence *in situ* hybridisation (FISH) testing confirmed a platelet-derived growth factor receptor alpha (PDGFRA) gene rearrangement. The patient was treated with 100 mg/day of imatinib; the eosinophilia resolved within 6 weeks.

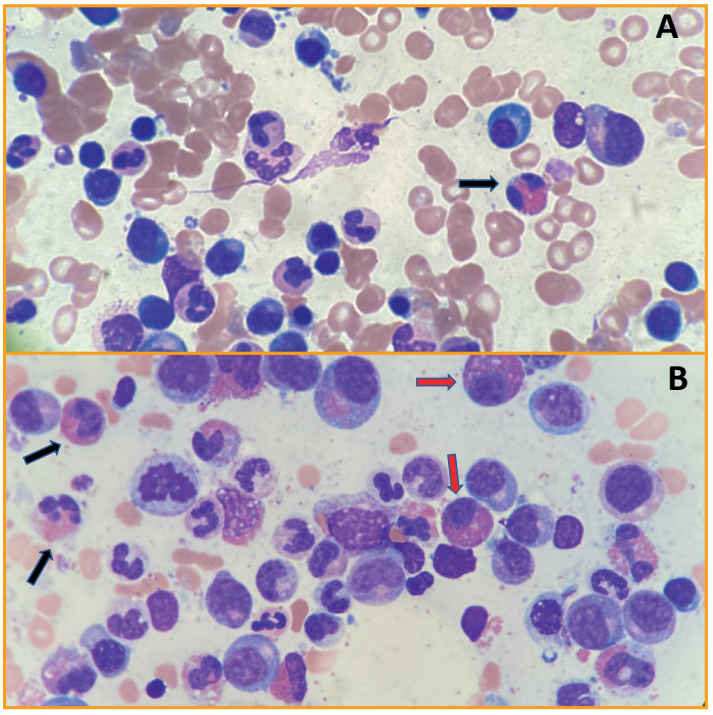

Figure 2. A. Normal bone marrow aspirate. A single mature eosinophil (dark arrow) noted surrounded by a plasma cell and maturing granulocytes. Wright-Giemsa stain, 1000X. B. Bone marrow aspirate from case 3 (Platelet-derived growth factor receptor alpha positive myeloproliferative disorder). Granulocytic hyperplasia and increased mature eosinophils (dark arrows) and eosinophil precursors (red arrows) present. Wright-Giemsa stain, 1000X.

Comment: This presentation underscores how target organ damage can rapidly occur in extreme eosinophilia. This patient presented with a tyrosine kinase inhibitor (TKI)-responsive myeloproliferative disorder (MPD) resulting from an interstitial deletion on chromosome 4 that resulted in the expression of the FIP1L1-PDGFRA fusion oncoprotein. The constitutively active PDGRFA is sensitive to TKI's at much lower doses than treating chronic myeloid leukemia. The new category designated by the World Health Organization of "myeloid and lymphoid neoplasms with eosinophilia and abnormalities of platelet-derived growth factor α (PDGFRA), platelet-derived growth factor β (PDGFRB), fibroblast growth factor receptor 1(*FGFR1*) or *PCM1-JAK2*" describes a number of diseases characterized by recurrent genetic translocation that result in constitutively activated tyrosine kinases and eosinophilia. Rearrangements involving *PDGFRA* and *PDGFRAB* are considered to be sensitive to TKI's[9,16-21].

Case 4: Eosinophilia presenting as a hypereosinophilic syndrome (HES)

A 23-year-old woman was diagnosed with a HES after presenting with wheezing, cough, chest pain, diarrhea, elevated troponins with an associated ST-elevation, and eosinophilia (5,100cells/μL). There were no precipitating causes[22]. Diagnostic criteria for EGPA were not met[23]. A bone marrow exam did not suggest a MPD, and both molecular and genetic testing did not confirm clonality. Flow cytometry was unable to detect $CD3^-$, $CD4^+$ lymphocytes. Other investigations confirmed eosinophilic bronchitis; colonoscopy confirmed eosinophilic infiltration, and cardiac MRI confirmed endocardial apical thickening and possible subendocardial involvement, suspicious for HES. Sinusitis was noted and nasal polyps were removed that were confirmed by histological exam to be infiltrated by eosinophils without vasculitis. Treatment with hydroxyurea and imatinib were discontinued due to intolerance. Mepolizumab was initiated and symptoms were controlled.

Comment: This case demonstrates the complexity of patients who present with eosinophilia and the need for care coordination among numerous specialties in order to establish a diagnosis. The patient had a number of diagnostic criteria for EGPA (sinusitis, pulmonary infiltrates, eosinophilia) but no evidence of vasculitis on biopsy and minimal evidence to support a diagnosis of asthma. Lymphoid-variant HES and myeloid causes were excluded. Infectious causes were excluded. Eosinophilic chronic rhinosinusitis (ECRS) is associated with the formation of nasal polyps, elevated IgE levels and eosinophilia through Th2-mediated mechanisms but not associated with tissue damage outside the upper airways[8]. A diagnosis of HES was made via persistent eosinophilia and target organ damage. The patient's response to mepolizumab is consistent with the published literature[24].

CONCLUSIONS

Eosinophilia can be a manifestation of an underlying complex disease. The history, medication profile, travel history and physical exam are important first steps in establishing diagnoses. Patients often require referral to specialists for further evaluation. In our center, we have established an interdisciplinary clinic to evaluate complex patients, allowing us to gain insight into the biology of these diseases. As an example, we have recently identified a group of patients presenting with eosinophilia and similar lung manifestations after noxious exposures where the patients also harbor identical exon 8 mutations in the *KIT* gene[25]. By working together with a multidisciplinary team to better understand the underlying etiology and complex biology involved with eosinophilia, we hope our patients will benefit and achieve optimal outcomes in disease management.

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