

Evaluation and Differential Diagnosis of Marked, Persistent Eosinophilia

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High-grade eosinophilia can be a diagnostic dilemma, as the etiologies are extensive and varied. Hypereosinophilic syndromes (HES) are a group of heterogeneous disorders, many of which remain poorly defined. By definition, HES must be distinguished from other disorders with persistently elevated eosinophilia with a defined cause. Although marked eosinophilia worldwide is most commonly caused by helminth (worm) infections, non-infectious causes must be considered, and include drug reactions, malignancies, and immunologic, inflammatory and allergic diseases. *Semin Hematol* 49:149–159. Published by Elsevier Inc.

Elevations in the levels of peripheral blood and tissue eosinophils can occur in a wide variety of disease processes that include infectious, allergic, neoplastic, primary hematologic disorders, and other, often less well-defined entities (Table 1). Worldwide, multicellular helminth (worm) parasites are most commonly associated with significant eosinophilia, followed in frequency by drug hypersensitivity and atopic diseases. Hypereosinophilic syndromes (HES), in contrast, are a set of relatively rare, heterogeneous disorders characterized by persistent eosinophilia and organ involvement/dysfunction in which other clinical entities have been excluded.¹ This definition of HES has been refined recently,² and HES are largely the subject of this issue of *Seminars in Hematology*. The approach to defining non-HES causes of persistently elevated eosinophilia is the focus of this particular contribution.

BIOLOGY OF THE EOSINOPHIL AND EOSINOPHILIA

Eosinophils are bone marrow-derived leukocytes whose development and terminal differentiation are under the control of several cytokines (interleukin [IL]-3, granulocyte-macrophage colony-stimulating fac-

tor [GM-CSF], and IL-5), with IL-5 being the cytokine that is primarily responsible for eosinophilopoiesis. Eosinophilia, defined as >450 eosinophils/ μL (or $500/\mu\text{L}$ in some studies) is normally measured by sampling peripheral blood, although eosinophils are predominantly found in peripheral tissues,³ particularly in those tissues with a mucosal-environmental interface such as the respiratory, gastrointestinal, and lower genitourinary tracts. Physiologically, eosinophil levels in the peripheral blood have a diurnal variation with a peak in the morning, a time at which endogenous steroids are the lowest.⁴ Pyogenic inflammation causes eosinopenia, a process that can mask the presence of eosinophilia or eosinophil-mediated inflammation. Hypoadrenalism is associated with eosinophilia because of low levels of endogenous glucocorticoids. Eosinophil levels can also be lowered by exogenous administration of medications, including corticosteroids, estrogen, and epinephrine.⁵

Eosinophils, particularly in disease states associated with hypereosinophilia, can have a variety of phenotypic and functional changes felt to reflect cellular activation (see Akuthota and Weller in this issue).

HYPEREOSINOPHILIC CONDITIONS

Based on more recent classifications of HES that include idiopathic hypereosinophilic syndrome (IHES), platelet-derived growth factor receptor α (PDGFR α)-associated myeloproliferative neoplasms, the lymphocytic variant HES (L-HES), familial hypereosinophilia, Churg-Strauss syndrome (CSS), and eosinophil-associated gastrointestinal disease (EGID), HES have been classified as heterogeneous group of uncommon disorders characterized by marked eosinophilia in the peripheral blood, tissues, or both, often without an identifiable cause.¹ It is against this backdrop that an

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This study was supported in part by the Division of Intramural Research (DIR) of the National Institute of Allergy and Infectious Diseases.

Financial disclosure: the authors have no financial relationships with commercial interests.

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0037-1963/\$ - see front matter

Published by Elsevier Inc.

doi:10.1053/j.seminhematol.2012.01.006

Table 1. Conditions Associated With Marked Peripheral Blood Eosinophilia*Infectious Diseases*

Parasitic infections primarily with helminths (see Table 2)

Certain fungal infections (allergic bronchopulmonary aspergillosis, coccidiomycosis)

Infestations—scabies, myiasis

Allergic or Atopic Diseases

Drug hypersensitivity or medication-associated eosinophilias

Atopic diseases

Hematologic and Neoplastic Disorders

Hypereosinophilic syndromes (HES) including chronic eosinophilic leukemia

Leukemia (acute myelogenous leukemias most commonly, B-cell acute lymphoblastic leukemia)

Lymphomas (particularly Hodgkin's, T- and B-cell lymphomas)

Tumor-associated

Adenocarcinomas

Squamous carcinomas

Large cell lung carcinomas

Transitional cell carcinoma of the bladder

Systemic mastocytosis

Immunologic

Primary immunodeficiency diseases (hyperIgE syndrome, Omenn syndrome, Dock8 deficiency, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome [IPEX], Zap70 deficiency)

Graft-versus-host disease

Endocrinologic Disorders

Hypoadrenalism

Other

Irradiation

Atheroembolic disorders

Sarcoidosis

approach to the differential diagnosis of those non-HES (with identifiable causes) associated with persistent, marked eosinophilia ($>1,500$ eosinophils/ μL) and/or evidence of organ involvement is discussed. Because there are comprehensive reviews of eosinophilia in general,⁶ the focus herein is on those disorders that could be confused with HES.

Infectious Diseases

A wide variety of infectious agents, almost exclusively helminth (worm) parasites, elicit eosinophilia⁷; only a relatively few, however, elicit a sustained,

marked increase in eosinophil levels (Table 2).⁸ The pattern and degree of eosinophilia in parasitic infections is determined by the development, migration, and distribution of the parasite within the host, as well as by the host's immune response. In general, it is useful to remember that parasites tend to elicit marked eosinophilia when they or their products come into contact with immune effector cells in tissues, particularly during migration. When barriers are erected between the parasite and host or when the parasite no longer invades tissue, the stimulus for eosinophilia is usually absent. Therefore, eosinophilia is highest in infections with a phase of parasite development that involves migration through tissue (eg, trichinosis, ascariasis, gnathostomiasis, strongyloidiasis, schistosomiasis, and filariasis), but a sustained eosinophilic response is not seen in parasites infections that are wholly intraluminal (eg, adult tapeworms) or contained in a cystic structure (eg, hydatid cysts) unless there is disruption of the integrity of the cyst wall with leakage of cyst contents and exposure to the immune system.⁹ Those parasites most likely to induce marked eosinophilia are noted in Table 2. Evaluation of helminth etiologies for marked eosinophilia should be guided not only by the clinical findings but also by the geographic history of potential exposures to infections. Approaches to the diagnosis of parasitic infections are suggested in Table 2 provided there is an appropriate exposure history.

Infections with protozoa rarely result in peripheral eosinophilia. However, the intestinal coccidian *Isospora belli* can be associated with eosinophilia.¹⁰ Less commonly, eosinophilia can result from infection with the protozoan *Dientamoeba fragilis*. Rarely, infection with *Sarcocystis hominis*, a cause of eosinophilic myositis, has been accompanied by marked peripheral eosinophilia.¹¹

Ectoparasites, particularly scabies, can also be associated with peripheral blood eosinophilia.¹² While eosinophilia has been noted in myiasis, this association occurs rarely.¹³ Although uncommon in human immunodeficiency virus (HIV) infection, modest eosinophilia can be seen. Marked hypereosinophilia has developed in some HIV-infected patients, particularly in those with a pustular, exfoliative dermatitis and eosinophilic folliculitis.¹⁴ Crusted or Norwegian scabies, more common in HIV and immunosuppressed patients, had higher mean levels of peripheral blood eosinophils compared to other ectoparasitic infections.¹⁵

Two fungal diseases also have been associated with hypereosinophilia: coccidiomycosis and aspergillosis (when presenting as allergic bronchopulmonary aspergillosis). Although the eosinophilia is typically mild in coccidial infections, marked eosinophilia may develop with disseminated coccidioidomycosis.¹⁶

Atopic/Allergic Diseases

Blood eosinophilia rarely exceeds $1,500/\mu\text{L}$ in allergic rhinitis, non-allergic rhinitis with eosinophilia syn-

Table 2. Helminth Infections Associated With Marked and/or Persistent Eosinophilia Parasitic Disease Development and Duration

Parasitic Disease Organism(s)	Development and Duration of Eosinophilia		Main Anatomical Site(s)	Diagnosis
	Acute	Persistent		
Angiostrongyloidiasis				
<i>Angiostrongylus cantonensis</i>	+		CNS	Larvae in CSF
<i>Angiostrongylus costaricensis</i>	+		GI	Biopsy
Ascariasis	+		GI	Eggs in stool
Clonorchiasis	+	+	Hepatobiliary	Eggs in stool, serology
Fascioliasis	+	+	Hepatobiliary	Eggs in stool, serology
Fasciolopsiasis	+		GI	Eggs in stool
Filarial infections				
Lymphatic filariasis				
<i>Brugia</i> , <i>Wuchereria</i>	+	+	Blood, lymphatics	Mf in blood, serology, CFA
<i>Loa loa</i>	+	+	Subcutaneous, eye	Mf in blood, worm extracted
<i>Mansonella ozzardi</i>	+	+	Blood	Mf in blood
<i>Mansonella perstans</i>	+	+	Blood, body cavities	Mf in blood, adult in tissue
<i>Mansonella streptocerca</i>	+	+	Skin, subcutaneous tissue	Mf in skin snips
<i>Onchocerca volvulus</i>	+	+	Skin, eye, subcutaneous tissue	Mf in skin snips, adults in nodules
Tropical pulmonary eosinophilia	+	+	Lung	Serology
Gnathostomiasis	+	+	Soft tissue	Serology, worm in specimen
Hookworm	+	+	GI, lung (acutely)	Eggs in stool
Opisthorchiasis	+	+	Hepatobiliary	Eggs in stool
Paragonimiasis	+	+	Lung, CNS, subcutaneous	Eggs in sputum, BAL, stool
Schistosomiasis	+			Serology
<i>Schistosoma haematobium</i>	+		Urinary tract	Eggs in urine, serology
<i>Schistosoma intercalatum</i>	+		Hepatic, GI	Eggs in stool
<i>Schistosoma japonicum</i>	+		Hepatic, GI	Eggs in stool
<i>Schistosoma mansoni</i>	+		Hepatic, GI	Eggs in stool, serology
<i>Schistosoma mekongi</i>	+		Hepatic, GI	Eggs in stool
Strongyloidiasis	+	+	GI, lung, skin	Larvae in stool, serology
Trichinosis	+	+	GI, muscle	Serology, muscle biopsy
Visceral larva migrans				
<i>Toxocara canis</i> ; <i>T. cati</i>	+	+	Liver, eye, lung	Serology, larvae in tissue
<i>Baylisascaris procyonis</i>	+	+	CNS, eye	Larvae in specimen

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; GI, gastrointestinal; Mf, microfilariae; CFA, circulating filarial antigen; BAL, bronchoalveolar lavage.

drome, or even in asthma (both allergic and non-allergic) despite respiratory tract eosinophil infiltration.¹⁷

Because many medications (as well as nutritional supplements) have been associated with eosinophilia, a detailed history of current and past medications should be obtained from all patients with eosinophilia. Although the mechanisms underlying the drug-associated rise in eosinophil levels have not been elucidated (apart

perhaps from some of the cytokines used therapeutically [eg, IL-2, GM-CSF]),^{18,19} medication-related drug reactions are the most common cause of persistently elevated eosinophil levels in areas of the world where exposure to helminth parasites is uncommon.⁸ Medication-associated peripheral blood eosinophilia may present without accompanying symptoms or may be associated with specific signs and symptoms. Asymptomatic

eosinophilia has been associated most often with quinine, penicillins, cephalosporins, and quinolones. Pulmonary infiltrates with peripheral eosinophilia have been particularly associated with nonsteroidal anti-inflammatory drugs (NSAIDs), sulfas, and nitrofurantoin. Drug-induced hepatitis with eosinophilia is most often induced by the tetracyclines or the semisynthetic penicillins, although more recently this has been seen with some of the atypical antipsychotics.²⁰ Eosinophilic pneumonia and peripheral blood eosinophilia have been associated with amiodarone, nitrofurantoin, and methotrexate but also rarely with serotonin and norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors.²¹ Interstitial nephritis with eosinophilia and eosinophiluria has been associated with cephalosporins (cefotaxime is most commonly reported, but others such as cefoxitin, cefoperazone, and ceftriaxone have also been implicated) and semisynthetic penicillins. Drug reaction with eosinophilia and systemic symptoms (DRESS) can occur with sulfasalazine, hydantoin, carbamazepine, D-penicillamine, allopurinol, hydrochlorothiazide, and cyclosporine, and can be associated with viral infection (human herpesvirus-6, Epstein-Barr virus, cytomegalovirus).²² Patients with DRESS present with fever, rash, systemic involvement, and an appropriate medication history. Various drug-associated eosinophilic disorders are listed in Table 3 and a more exhaustive list can be found elsewhere.⁶

Hematologic/Neoplastic

Lymphoid Malignancies

Apart from situations where eosinophils or their precursors are malignantly transformed, eosinophilia can be driven by the production of eosinophilopoietic cytokines. For example, eosinophilia is often associated with Hodgkin disease, and the generation of IL-5 by Reed-Sternberg cells has been demonstrated.²³ In primary cutaneous T-cell lymphoma and Sezary syndrome, blood and dermal eosinophilia are also frequently observed.²⁴

Solid Tumors

In addition to lymphomas, other neoplasms may occasionally be associated with blood eosinophilia. Tumor-associated eosinophilia occurs with large-cell nonkeratinizing cervical tumors, large-cell undifferentiated lung carcinomas,²⁵ squamous carcinomas of the lung, vagina, penis, skin, and nasopharynx,²⁶ adenocarcinomas of the stomach, large bowel, and uterine body, and transitional cell carcinoma of the bladder.²⁷

Mastocytosis

Systemic mast cell disease is accompanied by peripheral eosinophilia in about 25% of those with the

Table 3. Types of Drug Reactions Associated With Eosinophilia

Manifestations	Commonly Associated Drugs
Asymptomatic	Penicillins, cephalosporins
Soft tissue swelling	GM-CSF, IL-2
Pulmonary infiltrates	Nonsteroidal anti-inflammatory agents
Interstitial nephritis	Semisynthetic penicillins, cephalosporins
Myocarditis	Ranitidine
Hepatitis	Semisynthetic penicillins, tetracyclines
Hypersensitivity vasculitis	Allopurinol, phenytoin
Gastroenterocolitis	Nonsteroidal anti-inflammatory agents
Asthma, nasal polyps	Aspirin
Eosinophilia-myalgia syndrome	L-tryptophan contaminant
DRESS	Sulfasalazine, hydantoin, carbamazepine, allopurinol, hydrochlorothiazide, cyclosporine, nevaripine

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-2, interleukin-2; DRESS, drug reaction with eosinophilia and systemic symptoms.

disease.²⁸ Methods for distinguishing between HES (with mast cell involvement) and systemic mastocytosis with eosinophilia have been proposed.²⁹

Immunologic

Immunodeficiency Disorders

Among the many primary immunodeficiency disorders only a few are associated with high-grade eosinophilia: Omenn syndrome,³⁰ hyperIgE (Job) syndrome,³¹ Dock8 deficiency,³² immunodysregulation polyendocrinopathy enteropathy x-linked syndrome [IPEX],³³ and Zap70 deficiency.³⁴

Graft-Versus-Host Disease

Marked eosinophilia has also been seen occasionally with acute graft-versus-host disease (GVHD) and has been associated with milder GVHD and better outcomes.³⁵ Although chronic GVHD has also been associated with eosinophilia, particularly that which develops following allogeneic stem cell transplantation, the associated eosinophilia has not been shown to be of any prognostic value.³⁶

Endocrine

The loss of endogenous adrenoglucocorticosteroids in Addison disease, adrenal hemorrhage, or hypopituitarism can cause increased blood eosinophilia. Eosinophilia may help to make the diagnosis of adrenal insufficiency in some patients.³⁷

Other

Cholesterol embolization, typically after a vascular or intravascular procedure, can lead to eosinophilia.³⁸ Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy (EPPER) is characterized by tumor-associated blood eosinophilia and a cutaneous eosinophilic infiltrate.³⁹ Sarcoidosis, inflammatory bowel disease, and other disorders associated with immune dysregulation can also be associated with marked eosinophilia.⁴⁰

HYPEREOSINOPHILIA WITH ORGAN-RESTRICTED INVOLVEMENT

It is most important to be able to distinguish between HES and those conditions with overlapping clinical presentations. Because, historically, HES has required organ dysfunction associated with high-grade eosinophilia, known disorders of specific organ systems accompanied by eosinophilia are those most often confused with HES (see Table 4).

Skin and Subcutaneous Tissues

Atopic and Blistering Diseases

Eosinophils participate in the inflammatory infiltrate in numerous dermatologic conditions. Blood and tissue eosinophilia are common in atopic dermatitis.⁴¹ Tissue eosinophils are seen in blistering diseases, such as bullous pemphigoid, pemphigus vulgaris, dermatitis herpetiformis, and herpes gestationis, and can be prominent in drug-induced lesions. An uncommon disorder characterized by the association of nodules, eosinophilia, rheumatism, dermatitis, and swelling (NERDS), includes prominent para-articular nodules, recurrent urticaria with angioedema, and tissue and blood eosinophilia.⁴²

Eosinophilic Panniculitis

Eosinophilic panniculitis is characterized by a prominent eosinophil infiltration of subcutaneous fat.⁴³ Lesions often are nodular and less frequently present as plaques or vesicles. Eosinophilic panniculitis is commonly associated with gnathostomiasis, leukocytoclastic vasculitis, and erythema nodosum.⁴³ Other disorders associated with eosinophilic panniculitis include atopic and contact dermatitis, eosinophilic cellulitis, arthropod bites, toxocariasis, polyarteritis nodosa, injection granuloma, lupus panniculitis, malignancy, diabetes, and chronic recurrent parotitis.⁴³

Table 4. Diseases With Organ-Restricted Involvement and Marked Peripheral Eosinophilia

Skin and subcutaneous diseases
Episodic angioedema with eosinophilia
Eosinophilic cellulitis (Wells syndrome)
Eosinophilic panniculitis
Angiolymphoid hyperplasia with eosinophilia (and Kimura's disease)
Eosinophilic pustular dermatitis
Cutaneous necrotizing eosinophilic vasculitis
Pulmonary diseases
Drug- and toxin-induced eosinophilic lung diseases
Helminth-associated (Loeffler syndrome; tropical pulmonary eosinophilia)
Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia
Churg-Strauss syndrome
Other vasculitides
Gastrointestinal diseases
Eosinophilic gastrointestinal disorders (EGIDs)
Eosinophilic esophagitis (EE)
Eosinophilic gastroenteritis (EG)
Primary biliary cirrhosis
Sclerosing cholangitis
Eosinophilic cholangitis
Eosinophilic cholecystitis
Neurologic diseases
Eosinophilic meningitis
Ventriculoperitoneal shunts
Leukemia or lymphoma with CNS involvement (Hodgkin)
Nonsteroidal anti-inflammatory drugs
Antibiotics
Contrast agents
Rheumatologic diseases
Churg-Strauss syndrome
Other vasculitides
Eosinophilia-myalgia syndrome
Cardiac diseases
Hypersensitivity myocarditis
Churg-Strauss syndrome
Genitourinary disease
Drug induced interstitial nephritis
Eosinophilic cystitis

Episodic Angioedema With Eosinophilia

Although blood eosinophilia does not usually accompany angioedema, a distinct entity, episodic angioedema with eosinophilia is characterized by recurrent episodes of angioedema, urticaria, pruritus, fever, weight

gain with oliguria, elevated serum IgM, and leukocytosis with marked blood eosinophilia.⁴⁴ The level of blood eosinophilia parallels clinical symptoms. This disease is associated with cyclic alterations in serum IL-5 or GM-CSF levels.⁴⁵ The clinical course of this disease with its periodic recurrences of angioedema and eosinophilia distinguishes it from other forms of HES it is currently considered within the spectrum of HES.¹ Some patients will develop clonal T-cell populations that can progress to lymphocytic-variant HES.⁴⁶

Kimura's Disease and Angiolymphoid Hyperplasia With Eosinophilia

Kimura's disease presents as large subcutaneous masses on the head or neck of Asian men, whereas angiolymphoid hyperplasia with eosinophilia occurs in all races and is characterized by generally smaller and more superficial lesions. Eosinophilia is common to both.⁴⁷

Eosinophilic Fasciitis

Eosinophilic fasciitis (Shulman syndrome) has an acute onset of erythema, swelling, and induration of the extremities, often with a history of antecedent exercise.⁴⁸ Skin lesions are accompanied by elevated blood eosinophil counts. Histologically, unlike scleroderma, the epidermis and dermis are normal, with most pathology located in the subcutaneous tissue, fascia, and muscle.

Wells Syndrome (eosinophilic cellulitis)

Eosinophilic cellulitis is marked by recurrent swellings on the extremities.⁴⁹ Although involved skin appears cellitic, minimal tenderness, absence of warmth, and failure to respond to antibiotics distinguish it from bacterial cellulitis. It resolves spontaneously leaving a granulomatous infiltration. Blood eosinophilia is present in 50% of cases.

Eosinophilic Pustular Folliculitis

Mixed eosinophilic and neutrophilic infiltrates occur in affected follicles, and blood eosinophilia may be present.⁵⁰ Although described in healthy individuals, it also occurs in those infected with HIV and less commonly in HIV-negative patients being treated for hematologic malignancies or following bone marrow transplantation.⁵¹

Pulmonary

Eosinophilic lung diseases are a heterogeneous group of disorders unified by the presence of large numbers of eosinophils in the inflammatory cellular infiltrates in the airways or parenchyma of the lungs with a clinical presentation that usually consists of symptoms referable to the respiratory system accompanied by abnormal chest radiograph/computed to-

mography and peripheral blood eosinophilia. These eosinophilic lung diseases have been reviewed,⁵² and the major categories of pulmonary disorders associated with high-grade eosinophilia are listed in Table 4.

Besides the medication- and toxin-induced eosinophilic pulmonary diseases and allergic bronchopulmonary aspergillosis (discussed above), CSS, and helminth infections (particularly in the migratory phase early in the infection) have been associated with transient pulmonary infiltrates and marked eosinophilia (Loeffler syndrome).⁵³ Moreover, a very rare manifestation of *Wuchereria bancrofti*, termed "tropical pulmonary eosinophilia," is a systemic disorder defined by pulmonary infiltrates, nocturnal wheezing, IgE elevations, and marked peripheral eosinophilia.⁵⁴

Chronic Eosinophilic Pneumonia

This is a disease of unknown etiology that typically presents with cough, fever, dyspnea, and significant weight loss.⁵⁵ Laboratory findings include blood eosinophilia in almost 90% of patients.⁵⁵ Chronic eosinophilic pneumonia is characterized radiographically by peripheral infiltrates. Mediastinal lymphadenopathy may be present as well.

Histologically, lung biopsies show a predominantly eosinophilic infiltrate in the alveoli and interstitium.⁵⁶ Response to corticosteroid administration is dramatic, with blood eosinophilia often declining within 24 hours and complete resolution of symptoms occurring within 2 weeks in two thirds of patients.⁵⁵ Radiographic improvement may be seen as early as 60 to 72 hours, and radiologic clearance can be expected within 2 weeks in half of patients.⁵⁷ Recurrences of clinical and radiographic changes were seen in 58% of patients after discontinuation of corticosteroids.⁵⁵

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia is a clinical entity distinct from other eosinophilic pneumonias.⁵⁸ Patients commonly present with acute onset of cough, dyspnea, and fever. Diagnostic criteria for acute eosinophilic pneumonia have been defined and require both exclusion of other causes and the presence of a febrile illness of short duration, hypoxemic respiratory failure, diffuse alveolar or mixed alveolar-interstitial infiltrates on radiography, either bronchoalveolar lavage eosinophils >25% (or biopsy confirmation of lung tissue eosinophilia),⁵⁸ and rapid response to corticosteroids.

Gastrointestinal

Blood eosinophilia can develop in a number of gastrointestinal and hepatobiliary disorders, but tissue eosinophilia is more characteristic. The eosinophilic gastrointestinal diseases (EGID) have been discussed in full by Rothenberg et al.⁵⁹ In brief, there are a number of

gastrointestinal diseases that have eosinophil-mediated pathology and marked peripheral blood eosinophilia.

Eosinophilic Gastrointestinal Diseases

Eosinophilic Esophagitis (EoE). Characterized by eosinophilic infiltration of the esophagus, EoE is a disorder felt to have an unknown pathogenesis but with increasing evidence of Th2 dysregulation. Adults typically present with dysphagia and/or food impaction, and EoE should be considered in patients with these symptoms who do not improve on a proton pump inhibitor (PPI). Peripheral eosinophilia is common. Strictures may be seen on endoscopy; histopathology reveals mucosal infiltration with eosinophils. EoE was originally considered a symptom of gastroesophageal reflux disease (GERD), but small case studies using PPIs or H2 blockade failed to demonstrate definitive improvement in gastrointestinal mucosal eosinophil infiltrates. More large-scale double-blinded studies are still needed to provide a causal link between GERD and EoE.⁶⁰

Eosinophilic Gastroenteritis (EGE). EGE is an uncommon disorder characterized by nonspecific gastrointestinal symptoms, blood eosinophilia, and eosinophilic infiltration of the gastrointestinal wall. The peak age of onset is in the third to fourth decade and EGE has a male predominance. Allergies to foods, including milk, contribute in some children, but allergic etiologies are uncommon in adults. Different layers of the gastrointestinal tract may be involved, and, as a consequence, different types of symptoms may occur. Mucosal involvement can result in abdominal pain, nausea, vomiting, diarrhea, weight loss, anemia, protein-losing enteropathy, and intestinal perforation. Patients with muscular layer involvement have symptoms of pyloric or intestinal obstruction and early satiety. Subserosal eosinophilic infiltration may result in development of eosinophilic ascites due to eosinophilic infiltration of the pancreas.⁶¹

Hepatobiliary Diseases

Eosinophilic hepatitis develops in response to some medications⁶² and to helminth parasites (see Table 2). Marked peripheral eosinophilia has been seen in primary biliary cirrhosis (associated with early disease prior to elevated liver function tests⁶³), sclerosing cholangitis, eosinophilic cholangitis, and eosinophilic cholecystitis.⁶⁴ In 90% of cases, there is no evidence of parasitic infection and the peripheral eosinophilia is commonly drug-related or without a clear etiology.⁶⁵

Neurologic

Eosinophil-associated neurologic diseases are uncommon and include the disorders that cause eosinophilic meningitis.⁶⁶ Cerebrospinal fluid eosinophilia can be a significant clue to central nervous system

infections, ranging from fungal to helminthic (eg, coccidioidomycosis or *Angiostrongylus cantonensis* infection), as well as to adverse drug reactions to NSAIDs or antibiotics.

Rheumatologic

Marked peripheral blood eosinophilia is not common in connective tissue diseases, although it has been described in association with dermatomyositis,⁶⁷ rheumatoid arthritis, systemic sclerosis, and Sjögren syndrome.⁶⁸ It should be remembered that many of the drugs used to treat these disorders can cause hypersensitivity reactions with eosinophilia (eg, NSAIDs).

Eosinophilia-Myalgia Syndrome and Toxic Oil Syndrome

The eosinophilia-myalgia syndrome (EMS)⁶⁹ and toxic oil syndrome are both chronic, persistent multi-system diseases in which marked eosinophilia is present.⁷⁰ The toxic oil syndrome was due to ingestion of cooking oil adulterated with denatured rapeseed oil⁷¹ and an outbreak of EMS was associated with ingestion of contaminated L-tryptophan. Since 2005, there has only been one new case of EMS.⁷²

Vasculitis

Among the vasculitides, CSS is the disorder that is most commonly associated with high-grade, persistent eosinophilia.⁵² Although mild eosinophilia is common, marked eosinophilia is rare in many of the other vasculitides but has been seen in patients with cutaneous necrotizing vasculitis, thromboangiitis obliterans with eosinophilia of the temporal arteritis,⁷³ and Wegener's granulomatosis.⁷⁴

Cardiac

The principal cardiac sequela of eosinophilic diseases is damage to the endomyocardium.⁷⁵ This can occur with hypersensitivity myocarditis and with eosinophilias associated with eosinophilic leukemia, sarcomas, carcinomas, and lymphomas,⁷⁶ with GM-CSF¹⁹ or IL-2 administration,⁷⁷ with prolonged drug-induced eosinophilia, and with parasitic infections.⁷⁸

Genitourinary

Interstitial nephritis with eosinophilia is typically drug-induced. Agents known to induce nephritis include semisynthetic penicillins, cephalosporins, NSAIDs, allopurinol, rifampin, and ciprofloxacin.

Eosinophilic cystitis is a rare clinicopathological condition characterized by transmural inflammation of the bladder predominantly with eosinophils. It has been associated with bladder tumors, bladder trauma, parasitic infections, and some medications. The most

common symptom complex consists of urinary frequency, hematuria, dysuria, and suprapubic pain.⁷⁹

APPROACH TO THE EVALUATION OF A PATIENT WITH HIGH-GRADE EOSINOPHILIA

The approach to identifying the cause of marked, persistent eosinophilia is a challenging problem. Nevertheless, the prevention of morbidity by identifying the cause of the eosinophilia and intervening therapeu-

tically is an important task that should be approached systematically. Although this article assumes that the presence of marked eosinophilia has been established, it should be borne in mind that some of the earlier automated methods used to assess leukocyte populations were inaccurate in establishing the presence of eosinophilia.

To evaluate a patient with persistent and marked eosinophilia, the approach suggested in Table 5 is recommended. A careful history should be taken directed

Table 5. Approach to Evaluation of Marked Eosinophilia

Eosinophil Determinations—Verify eosinophil count; estimate or get absolute eosinophil count

Medical History

- Obtain history of previous eosinophil counts
- Medical history
 - Review medical history with emphasis placed on disorders known to be associated with eosinophilia including atopic disease
- Medication history
 - Review recent and current medication history
 - Discontinue any drugs known to be associated with eosinophilia
 - Make a detailed list of all medications (including nutritional supplements, vitamins, herbal preparations)
 - Note any history of allergy to medications
- Travel/geographic history
 - Review past history of travel to or residence in other countries
 - Review travel within indigenous country with emphasis on regions where particular eosinophilia-associated infections may be common
- Occupational/recreational history
 - Review occupational and recreational exposures
- Dietary history
 - Review carefully; query dietary indiscretions, nutritional supplements
- Family history
 - Review whether others in family have eosinophilia suggesting a common exposure or familial nature of disease

Physical Examination

- Do a careful physical examination
- Close attention paid to skin, soft tissues, masses, lymphadenopathy

Initial Laboratory Evaluation

- Routine studies to assess general hematologic status (CBC, platelet count)
- Studies to assess organ function (liver function tests, renal function tests, urinalysis, chest radiograph), inflammation (CRP/ESR), immune status (immunoglobulins, IgE).

Further Diagnostic Evaluations (based on initial laboratory findings or localizing symptoms)

- Tissue examination (biopsies) if necessary
- Specimen collection (CSF, sputum, bronchoalveolar lavage, stool, urine)
- CT and MRI to define better focal lesions.
- Bone marrow aspirates and biopsies to assess fully the nature of the process underlying the eosinophilia.
- Additional disease-defining tests to exclude particular diagnoses (e.g. serum tryptase/cKIT mutations for systemic mastocytosis, antineutrophil cytoplasmic antibodies (ANCA) for CSS and other vasculitides, serologies for helminthes)

Abbreviations: CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; CSS, Churg-Strauss syndrome.

specifically at the nature of the symptoms (if present) with an emphasis placed on disorders known to be associated with eosinophilia, previous eosinophil counts (if available), and travel, occupational, and dietary history. A complete medication history should be taken that includes over-the-counter medications, supplements, herbal preparations, and vitamins; any medication known to induce eosinophilia should be discontinued. Patients should be asked about diseases commonly found in their family; previous allergies to medications or to environmental allergens must also be addressed.

Physical examination with special attention to skin, soft tissues, lungs, liver, and spleen, as well as an additional directed examination based on the patient's specific symptoms or chief complaints, is obviously important.

Initially, the approach to the evaluation of marked eosinophilia must be to assess general health status and to assess whether there is underlying organ dysfunction. The eosinophilia must be confirmed, and an estimation of the absolute eosinophil count (if not measured directly) must be made. Routine studies to assess hematologic status (complete blood cell count, platelet count, prothrombin time/partial thromboplastin time), studies to assess organ function (liver function tests, renal function tests, urinalysis, chest radiograph or computed tomography, electrocardiogram), markers of inflammation (C-reactive protein/erythrocyte sedimentation rate) and immunologic status (quantitative immunoglobulins and IgE) should also be performed routinely. The presence of particular symptoms or physical findings may direct other laboratory studies.

Further diagnostic evaluations based on the initial studies are usually required to distinguish among the myriad of disorders underlying hypereosinophilia. When a parasitic infection is suspected, the laboratory evaluation should be based on information gleaned from the history and physical examination in order to avoid going on a "fishing expedition" by ordering needless laboratory tests; however, a minimum set of diagnostic tests directed toward establishing the presence of a particular parasite should be obtained (Table 3). The localizing clinical findings in symptomatic patients, as well as laboratory evidence of organ involvement, must guide the subsequent evaluation. Access to tissue (biopsies) or material (eg, cerebrospinal fluid, sputum, bronchoalveolar lavage, stool, urine) that can identify the underlying problem is often necessary. Computed tomography and magnetic resonance imaging to define better focal lesions should be employed. Bone marrow aspirates and biopsies will often be necessary to assess fully the nature of the process underlying the markedly elevated eosinophil count. Additional disease-defining tests may be necessary to exclude particular diagnoses (eg, serum tryptase/assessment of cKIT mutations for systemic mastocytosis, antineutrophil cytoplasmic anti-

bodies for CSS and other vasculitides, serologies for helminths).

CONCLUSION

The approach to the identifying the cause of marked, persistent eosinophilia is a challenging problem. Excluding many of these non-HES causes of marked peripheral blood eosinophilia is required for making the diagnosis of HES. Moreover, the prevention of morbidity by identifying the cause of the eosinophilia and intervening therapeutically is an important task that must be approached systematically.

REFERENCES

1. Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol*. 2006;117:1292-302.
2. Simon HU, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010;126:45-9.
3. Weller PF. The immunobiology of eosinophils. *N Engl J Med*. 1991;324:1110-8.
4. Uhrbrand H. The number of circulating eosinophils; normal figures and spontaneous variations. *Acta Med Scand*. 1958;160:99-104.
5. Beeson PB, Bass DA. The eosinophil. *Major Probl Intern Med*. 1977;14:1-269.
6. Weller PF. Eosinophilia and eosinophil-related disorders. In: Adkinson NF, Yunginger JW, Busse WW, et al. (eds). *Allergy: principles and practices*. 6th ed. St. Louis: Mosby-Year Book; 2003:1105-555.
7. Weller PF. Eosinophilia in travelers. *Med Clin North Am*. 1992;76:1413-32.
8. Nutman TB. Evaluation and differential diagnosis of marked, persistent eosinophilia. *Immunol Allergy Clin North Am*. 2007;27:529-49.
9. Moore TA, Nutman TB. Eosinophilia in the returning traveler. *Infect Dis Clin North Am*. 1998;12:503-21.
10. Trier JS, Moxey PC, Schimmel EM, Robles E. Chronic intestinal coccidiosis in man: intestinal morphology and response to treatment. *Gastroenterology*. 1974;66:923-35.
11. Chen X, Zuo Y, Zuo W. [Observation on the clinical symptoms and sporocyst excretion in human volunteers experimentally infected with *Sarcocystis hominis*]. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi*. 1999;17:25-7.
12. Deshpande AD. Eosinophilia associated with scabies. *Practitioner*. 1987;231:455.
13. Starr J, Pruett JH, Yunginger JW, Gleich GJ. Myiasis due to *Hypoderma lineatum* infection mimicking the hypereosinophilic syndrome. *Mayo Clin Proc*. 2000;75:755-9.
14. Nervi SJ, Schwartz RA, Dmochowski M. Eosinophilic pustular folliculitis: a 40 year retrospect. *J Am Acad Dermatol*. 2006;55:285-9.
15. Roberts LJ, Huffam SE, Walton SF, Currie BJ. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. *J Infect*. 2005;50:375-81.

16. Harley WB, Blaser MJ. Disseminated coccidioidomycosis associated with extreme eosinophilia. *Clin Infect Dis*. 1994;18:627-9.
17. Settipane GA, Klein DE. Non allergic rhinitis: demography of eosinophils in nasal smear, blood total eosinophil counts and IgE levels. *N Engl Reg Allergy Proc*. 1985;6:363-6.
18. Ishimitsu T, Torisu M. The role of eosinophils in interleukin-2/lymphokine-activated killer cell therapy. *Surgery*. 1993;113:192-9.
19. Donhuijsen K, Haedicke C, Hattenberger S, et al. Granulocyte-macrophage colony-stimulating factor-related eosinophilia and Loeffler's endocarditis. *Blood*. 1992;79:2798.
20. Dumortier G, Cabaret W, Stamatiadis L, et al. [Hepatic tolerance of atypical antipsychotic drugs]. *Encephale*. 2002;28:542-51.
21. Allen JN. Drug-induced eosinophilic lung disease. *Clin Chest Med*. 2004;25:77-88.
22. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124:588-97.
23. Gruss HJ, Brach MA, Drexler HG, et al. Expression of cytokine genes, cytokine receptor genes, and transcription factors in cultured Hodgkin and Reed-Sternberg cells. *Cancer Res*. 1992;52:3353-60.
24. Borish L, Dishuck J, Cox L, et al. Sezary syndrome with elevated serum IgE and hypereosinophilia: role of dysregulated cytokine production. *J Allergy Clin Immunol*. 1993;92:123-31.
25. Knox AJ, Johnson CE, Page RL. Eosinophilia associated with thoracic malignancy. *Br J Dis Chest*. 1986;80:92-5.
26. Lowe D, Fletcher CD. Eosinophilia in squamous cell carcinoma of the oral cavity, external genitalia and anus—clinical correlations. *Histopathology*. 1984;8:627-32.
27. Lowe D, Fletcher CD, Gower RL. Tumour-associated eosinophilia in the bladder. *J Clin Pathol*. 1984;37:500-2.
28. Parker RI. Hematologic aspects of systemic mastocytosis. *Hematol Oncol Clin North Am*. 2000;14:557-68.
29. Maric I, Robyn J, Metcalfe DD, et al. KIT D816V-associated systemic mastocytosis with eosinophilia and FIP1L1/PDGFR α -associated chronic eosinophilic leukemia are distinct entities. *J Allergy Clin Immunol*. 2007;120:680-7.
30. Aleman K, Noordzij JG, de Groot R, et al. Reviewing Omenn syndrome. *Eur J Pediatr*. 2001;160:718-25.
31. Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007;357:1608-19.
32. Zhang Q, Davis JC, Lamborn IT, et al. Combined immunodeficiency associated with DOCK8 mutations. *N Engl J Med*. 2009;361:2046-55.
33. Gambineri E, Perroni L, Passerini L, et al. Clinical and molecular profile of a new series of patients with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome: inconsistent correlation between forkhead box protein 3 expression and disease severity. *J Allergy Clin Immunol*. 2008;122:1105-12.
34. Turul T, Tezcan I, Artac H, et al. Clinical heterogeneity can hamper the diagnosis of patients with ZAP70 deficiency. *Eur J Pediatr*. 2009;168:87-93.
35. Imahashi N, Miyamura K, Seto A, et al. Eosinophilia predicts better overall survival after acute graft-versus-host-disease. *Bone Marrow Transplant*. 2010;45:371-7.
36. Ahmad I, Labbe AC, Chagnon M, et al. Incidence and prognostic value of eosinophilia in chronic graft-versus-host disease after nonmyeloablative hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2011;17:1673-8.
37. Beishuizen A, Vermes I, Hylkema BS, Haanen C. Relative eosinophilia and functional adrenal insufficiency in critically ill patients. *Lancet*. 1999;353:1675-6.
38. Wilson DM, Salazer TL, Farkouh ME. Eosinophiluria in atheroembolic renal disease. *Am J Med*. 1991;91:186-9.
39. Rueda RA, Valencia IC, Covelli C, et al. Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy. *Arch Dermatol*. 1999;135:804-10.
40. Renston JP, Goldman ES, Hsu RM, Tomasheski JF. Peripheral blood eosinophilia in association with sarcoidosis. *Mayo Clin Proc*. 2000;75:586-90.
41. Leiferman KM. Eosinophils in atopic dermatitis. *J Allergy Clin Immunol*. 1994;94:1310-7.
42. Butterfield JH, Leiferman KM, Gleich GJ. Nodules, eosinophilia, rheumatism, dermatitis and swelling (NERDS): a novel eosinophilic disorder. *Clin Exp Allergy*. 1993;23:571-80.
43. Adame J, Cohen PR. Eosinophilic panniculitis: diagnostic considerations and evaluation. *J Am Acad Dermatol*. 1996;34:229-34.
44. Gleich GJ, Schroeter AL, Marcoux JP, et al. Episodic angioedema associated with eosinophilia. *N Engl J Med*. 1984;310:1621-6.
45. Banerji A, Weller PF, Sheikh J. Cytokine-associated angioedema syndromes including episodic angioedema with eosinophilia (Gleich's syndrome). *Immunol Allergy Clin North Am*. 2006;26:769-81.
46. Gonzalez Delgado P, de la Sen Fernandez ML, Soriano Gomis V, et al. Cyclical hypereosinophilia with skin manifestations and a clonal T cell population. *J Invest Allergol Clin Immunol*. 2008;18:401-3.
47. Abuel-Haija M, Hurford MT. Kimura disease. *Arch Pathol Lab Med*. 2007;131:650-1.
48. Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? *Trans Assoc Am Physicians*. 1975;88:70-86.
49. Espana A, Sanz ML, Sola J, Gil P. Wells' syndrome (eosinophilic cellulitis): correlation between clinical activity, eosinophil levels, eosinophil cation protein and interleukin-5. *Br J Dermatol*. 1999;140:127-30.
50. McCalmont TH, Altomus D, Maurer T, Berger TG. Eosinophilic folliculitis. The histologic spectrum. *Am J Dermatopathol*. 1995;17:439-46.
51. Basarab T. HIV-associated eosinophilic pustular folliculitis. *J Am Acad Dermatol*. 1997;37:670-1.
52. Wechsler ME. Pulmonary eosinophilic syndromes. *Immunol Allergy Clin North Am*. 2007;27:477-92.
53. Loeffler W. Transient lung infiltrations with blood eosinophilia. *Int Arch Allergy Appl Immunol*. 1956;8:54.
54. Ottesen EA, Nutman TB. Tropical pulmonary eosinophilia. *Annu Rev Med*. 1992;43:417-24.
55. Jederlinic PJ, Sicilian L, Gaensler EA. Chronic eosino-

- philic pneumonia. A report of 19 cases and a review of the literature. *Medicine*. 1988;67:154–62.
56. Olopade CO, Crotty TB, Douglas WW, et al. Chronic eosinophilic pneumonia and idiopathic bronchiolitis obliterans organizing pneumonia: comparison of eosinophil number and degranulation by immunofluorescence staining for eosinophil-derived major basic protein. *Mayo Clin Proc*. 1995;70:137–42.
57. Mayo JR, Muller NL, Road J, et al. Chronic eosinophilic pneumonia: CT findings in six cases. *AJR Am J Roentgenol*. 1989;153:727–30.
58. Allen JA, Pacht ER, Gadek JE, Davis WB. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. *N Engl J Med*. 1989;321:569–74.
59. Zuo L, Rothenberg ME. Gastrointestinal eosinophilia. *Immunol Allergy Clin North Am*. 2007;27:443–55.
60. Almansa C, Devault KR, Achem SR. A comprehensive review of eosinophilic esophagitis in adults. *J Clin Gastroenterol*. 2011;45:658–64.
61. de Chambrun GP, Gonzalez F, Canva JY, et al. Natural history of eosinophilic gastroenteritis. *Clin Gastroenterol Hepatol*. 2011;9:950–6.
62. Fix OK, Peters MG, Davern TJ. Eosinophilic hepatitis caused by lamotrigine. *Clin Gastroenterol Hepatol*. 2006;4:A26.
63. Terasaki S, Nakanuma Y, Yamazaki M, Unoura M. Eosinophilic infiltration of the liver in primary biliary cirrhosis: a morphological study. *Hepatology*. 1993;17:206–12.
64. Rosengart TK, Rotterdam H, Ranson JH. Eosinophilic cholangitis: a self-limited cause of extrahepatic biliary obstruction. *Am J Gastroenterol*. 1990;85:582–5.
65. Shakov R, Simoni G, Villacin A, Baddoura W. Eosinophilic cholecystitis, with a review of the literature. *Ann Clin Lab Sci*. 2007;37:182–5.
66. Graeff-Teixeira C, da Silva AC, Yoshimura K. Update on eosinophilic meningoencephalitis and its clinical relevance. *Clin Microbiol Rev*. 2009;22:322–48.
67. Kargili A, Bavbek N, Kaya A, et al. Eosinophilia in rheumatologic diseases: a prospective study of 1000 cases. *Rheumatol Int*. 2004;24:321–4.
68. Bavbek N, Kargili A, Cipil H, et al. Rheumatologic disease with peripheral eosinophilia. *Rheumatol Int*. 2004;24:317–20.
69. Belongia EA, Hedberg CW, Gleich GJ, et al. An investigation of the cause of the eosinophilia-myalgia syndrome associated with tryptophan use. *N Engl J Med*. 1990;323:357–65.
70. Kaufman LD, Gleich GJ. The expanding clinical spectrum of multisystem disease associated with eosinophilia. *Arch Dermatol*. 1997;133:225–7.
71. Patterson R, Germolec D. Review article toxic oil syndrome: review of immune aspects of the disease. *J Immunotoxicol*. 2005;2:51–8.
72. Allen JA, Peterson A, Sufit R, et al. Post-epidemic eosinophilia myalgia syndrome associated with L-tryptophan. *Arthritis Rheum*. 2011;63:3633–9.
73. Ito K, Hara H, Okada T, Terui T. Hypereosinophilic syndrome with various skin lesions and juvenile temporal arteritis. *Clin Exp Dermatol*. 2009;34:e192–5.
74. Shoda H, Kanda H, Tanaka R, et al. Wegener's granulomatosis with eosinophilia. *Intern Med*. 2005;44:750–3.
75. Ogbogu PU, Rosing DR, Horne MK 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. *Immunol Allergy Clin North Am*. 2007;27:457–75.
76. Monsuez JJ, de Kerviler E, Barboteu M, et al. Non-Hodgkin's lymphoma related eosinophilic endomyocardial disease. *Eur Heart J*. 1994;15:1423–7.
77. Junghans RP, Manning W, Safar M, Quist W. Biventricular cardiac thrombosis during interleukin-2 infusion. *N Engl J Med*. 2001;344:859–60.
78. Andy JJ, Bishara FF, Soyinka OO, Odesanmi WO. Loiasis as a possible trigger of African endomyocardial fibrosis: a case report from Nigeria. *Acta Tropica*. 1981;38:179–86.
79. van den Ouden D. Diagnosis and management of eosinophilic cystitis. *Eur Urol*. 2000;37:386–94.