

Hypereosinophilic syndrome

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ABSTRACT

Background: Hypereosinophilic syndrome (HES) is a myeloproliferative disorder characterized by persistent eosinophilia associated with multiple organ damage.

Objective: To increase awareness of the rare but potentially life-threatening disease and to provide a brief overview of the clinical presentation, diagnosis, and management of HES.

Methods: Pertinent data from the patient's clinical course was incorporated with salient articles on the topic.

Results: A case of HES is presented, followed by discussion of the clinical characteristics, diagnosis, and management. Clinical pearls and pitfalls are emphasized for the practicing allergist, clinical immunologist, and fellow-in-training.

Conclusion: A diagnosis of HES should be considered in patients with an absolute eosinophil count of >1500 cells/ μL documented on two occasions at least 1 month apart, and/or in those with pathologic confirmation of tissue hypereosinophilia. The decision to treat HES should be guided by both the clinical presentation and results of laboratory and mutational analysis.

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Question:

A previously healthy 64-year-old man presented to an allergy clinic in rural South Carolina with a chief concern of progressive shortness of breath and chest discomfort. He had been in his usual state of health until 6 months earlier when he presented to the emergency department for acute shortness of breath. His history and presentation were unremarkable, except for a 30 pack-year history of tobacco smoking (he had quit more than a decade ago) and previous nasal polypectomy. He was not on any medication and had no history of allergies, recent travel, illnesses, or diet changes. He was diagnosed with bronchitis and discharged with bronchodilators and steroids. Over the subsequent month, he was formally diagnosed with chronic obstructive pulmonary disease, hypertension, and, later, with myopericarditis. Results of studies done just before the allergy clinic visit were notable for pericardial effusion, decreased ejection fraction, an absolute eosinophil count of 2300 cells/ μL , elevated C-

reactive protein level, and high erythrocyte sedimentation rate. He was compliant with his prescription medications. During the visit, the patient had persistent chest discomfort, appetite loss, and unintended weight loss. Results of a physical examination were unremarkable. Initial laboratory results showed an absolute eosinophil count of 20,000 cells/ μL , with normal electrolyte and creatinine levels. Which of the following is true?

Answer Choices:

A. The patient should start imatinib immediately while awaiting Fip1-like1-platelet-derived growth factor receptor α (*FIP1L1-PDGFR α*) fusion gene test results.

B. The patient should start prednisone first and switch to mepolizumab if the *FIP1L1-PDGFR α* test results come back negative.

C. The *FIP1L1-PDGFR α* associated variant of hypereosinophilic syndrome affects both sexes in equal proportions.

D. The lungs are the most frequently affected organ and cause of morbidity and mortality of hypereosinophilic syndrome.

E. The patient should start corticosteroid and empiric ivermectin while awaiting *Strongyloides* test results.

Hypereosinophilic syndrome (HES) is a disease characterized by the following: (a) a persistent absolute eosinophil count (AEC) of >1500 cells/ μL documented on two occasions at least 1 month apart and/or pathologic confirmation of tissue hypereosinophilia,

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Table 1 Manifestations of hypereosinophilic syndrome and relative frequency of report*

Clinical Manifestations on Initial Presentation	Frequency of Report, %	Description
Dermatologic	37	Urticaria, angioedema, pruritus, dermatitis, erythroderma, bullous lesions, eosinophilic cellulitis, unspecified edema, mucosal erosions
Pulmonary	25	Asthma, sinusitis, rhinitis, cough, dyspnea, recurrent upper respiratory infection, pulmonary infiltrates, pleural effusion
Gastrointestinal	14	Abdominal pain, vomiting, diarrhea
Rheumatologic	7	Arthralgia, myalgia, arthritis, myositis
Routine laboratory test	6	Incidental abnormality found on routine laboratory testing
Constitutional	5	Fever, weight loss, malaise, fatigue, night sweats, flulike illness
Neurologic	5	Vertigo, paresthesia, change in mentation, aphasia, visual disturbances
Cardiac	5	Congestive heart failure, valvular abnormality, cardiomyopathy, pericardial effusion, myocarditis
Hematologic	3	Deep venous thrombosis, anemia, superficial thrombophlebitis

*Adapted from a table in Ref. 3.

(b) evidence of eosinophil-mediated organ damage or dysfunction, and (c) other potential causes of the damage have been ruled out.¹ Thus, the term can be used even if the cause of eosinophilia is known, *e.g.*, leukemia, provided that eosinophilic tissue infiltration is the mechanism of injury. HES is a rare disease that affects 0.36–6.3 per 100,000 people, and most patients are diagnosed at 20–50 years of age. Although men are affected predominantly in certain types of HES, such as that caused by the *FIP1L1-PDGfra* fusion gene, other types of HES affect both men and women in equal proportions.^{2,3}

CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

A retrospective multicenter study of 188 patients with HES revealed that the disease can affect multiple organ systems, including skin, lungs, and the gastrointestinal tract (Table 1). Less frequent are the rheumatologic, neurologic, and cardiac manifestations. Of all these, dermatologic manifestations are the most common, and the most significant morbidity and mortality are observed with cardiac complications.^{3,4} Pathophysiology of HES involves eosinophil overproduction and infiltration that leads to tissue damage. There currently are two theories on how derangement of eosinophil production occurs in HES: (a) overproduction of regulatory cytokines, such as interleukin-5 (IL-5), and (b) clonal proliferation due to an error or defect in signal transduction or in hematopoietic stem cells.⁴

Several variants of HES have been identified so far. For example, the T-cell lymphocytic variant HES is thought to involve IL-5-producing T cells and is usually characterized by skin findings. The myeloproliferative HES variants, however, have features such as

high serum B12, anemia, thrombocytopenia, hepatosplenomegaly, and chromosomal abnormalities. The most frequently observed gene aberration is the *FIP1L1-PDGfra* fusion gene, which displays constitutive tyrosine kinase activity, and is thought to lead to eosinophil overproduction. There is also a familial form of HES that is transmitted in autosomal dominant fashion. Some cases of HES are restricted to a single organ or are associated with a specific syndrome, such as collagen vascular disease. Also, a large portion of HES cases are diagnosed as an idiopathic variant despite careful evaluation.^{4,5}

DIAGNOSIS

Because HES is mainly a diagnosis of exclusion, a thorough evaluation is warranted in any patient with an AEC of >1500 cells/ μ L on at least two different occasions even if the patient is asymptomatic. Although history and physical examination results will help the clinician tailor the workup, commonly recommended initial studies are blood chemistry, stool ova and parasite, *Strongyloides* serology test, chest radiography, pulmonary function testing, echocardiography, electrocardiography, computed tomography studies, tissue biopsy, assorted molecular testing, and serum biomarkers (*e.g.*, vitamin B₁₂, immunoglobulins, or tryptase). A list of causes of hypereosinophilia is provided in Table 2 and includes disorders that are not detailed in this article.⁶

MANAGEMENT

Treatment of HES depends on both the severity of the illness and on the HES variant.^{4,5} Prompt treatment with high-dose glucocorticoid, *e.g.*, prednisone at 1

Table 2 Differential diagnosis of hypereosinophilia*

Infectious disease
Parasitic: Strongyloidiasis, trichinellosis, toxocariasis, filariasis
Specific fungal infections, <i>e.g.</i> , coccidiomycosis
Infrequent causes, <i>e.g.</i> , human immunodeficiency virus, human T-lymphotropic virus
Hematologic and neoplastic disorders
Systemic mastocytosis with eosinophilia
Leukemia
Lymphoma
Solid tumors
Allergic disorders
Drug hypersensitivity reaction
Atopy and related conditions
Endocrine
Adrenal insufficiency
Organ-specific diseases
Lungs: Allergic bronchopulmonary aspergillosis, idiopathic eosinophilic pneumonia
Skin: Dermatitis herpetiformis, bullous pemphigoid
Gastrointestinal: Eosinophilic esophagitis, eosinophilic gastroenteritis, inflammatory bowel disease
Vascular: Churg-Strauss syndrome (also called eosinophilic granulomatosis with polyangiitis)
Rheumatologic: Systemic lupus erythematosus
Immunologic disorders
Hyperimmunoglobulin E syndrome (Job syndrome)
Hyperimmunoglobulin M syndrome
Selective immunoglobulin A deficiency
Transplantation rejection

*Adapted from Ref. 4.

mg/kg, is indicated in severe cases of patients who present with extreme hypereosinophilia (AEC > 100,000 cell/ μ L), signs and symptoms of leukostasis, or other life-threatening complications (Table 3). It is particularly important that a risk assessment for strongyloidiasis be done before corticosteroid treatment. Although helminths are the most common parasitic cause of hypereosinophilia and several types are endemic worldwide, *Strongyloides stercoralis* is notable for the association between corticosteroid treatment and subsequent fatal disseminated strongyloidiasis in patients who are otherwise immunocompetent. It is believed that the hyperinfection syndrome triggered by corticosteroid is linked to the unique life cycle of the parasite, which is capable of autoinfection. Corticosteroid administration should not be delayed, however, and empiric ivermectin of 200 μ g/kg daily for 2 days can be administered simultaneously with steroids if strongyloidiasis is suspected.⁴

Table 3 Indications for prompt corticosteroid therapy in patients with hypereosinophilia*

Concern for hypereosinophilia-induced organ damage, <i>e.g.</i> , clinical evidence or laboratory markers that indicate eosinophilic cardiomyopathy, findings of thromboemboli that affect the central nervous system
Exceedingly high level of eosinophilia (<i>e.g.</i> , absolute eosinophil count of >100,000 cells/ μ L)
Clinical evidence and study results that are concerning for leukostasis

*Adapted from Ref. 5.

In cases in which emergent treatments are not indicated, the decision to either carefully monitor a patient or to start therapy depends on both clinical symptoms and the HES variant. Regardless of the decision, all patients with suspected HES must be regularly monitored for organ damage, cardiovascular and thromboembolic complications, and disease progression. If a myeloproliferative variant of HES is suspected due to findings such as high serum B₁₂, anemia, thrombocytopenia, hepatosplenomegaly, or chromosomal abnormalities, then therapy should start with imatinib mesylate as the first-line treatment. Imatinib mesylate is a tyrosine kinase inhibitor that effectively treats *FIP1L1-PDGFR* fusion-related myeloproliferative HES.^{5,7}

For HES without myeloproliferative features, corticosteroids or management of the underlying condition is the first-line treatment. Once initial hypereosinophilia and symptoms are suppressed, corticosteroid should be tapered to the lowest allowable amount, and a steroid-sparing agent should be considered if the prednisone dose exceeds 10 mg per day or if the patient experiences adverse effects from the treatment. Hydroxyurea, imatinib, and interferon α are available second-line agents. There is limited experience with hematopoietic cell transplantation or drugs such as vincristine, cyclophosphamide, or methotrexate. Investigational agents such as humanized IL-5 antibodies (*e.g.*, mepolizumab) or IL-5 receptor antibodies (*e.g.*, benralizumab) are currently showing promise in clinical trials.⁸

Also, the patients of asymptomatic hypereosinophilia without myeloproliferative features do not warrant therapy at the time of diagnosis. However, even such patients need regular monitoring to detect any disease progression and to initiate appropriate therapy. In terms of prognosis, favorable features include corticosteroid responsiveness, the absence of cardiac or neurologic complications, and a lower AEC. In contrast, features associated with myeloproliferative variant HES portend a poorer prognosis. Early case series of HES from 1975 noted a mean survival of only 9

months, with many deaths attributed to heart failure in the setting of advanced disease.⁹ In contrast, a French study from 1989 showed a 5-year survival rate of 80%, which reflects improved longevity of patients with HES due to early detection and better management options.¹⁰ Furthermore, more recent studies also support reduced mortality of both myeloproliferative and nonmyeloproliferative variant HES because of new and targeted therapies.^{7,8}

Answers to the Question:

- A. False. Given the severity of the disease presentation in this patient, corticosteroids are the first-line treatment.
- B. False. If the *FIP1L1-PDGFR*A test result is negative, then corticosteroid is the first-line treatment. Second-line agents, *e.g.*, imatinib, can be considered for corticosteroid-sparing effect after reaching a minimal maintenance dose of glucocorticoid. Mepolizumab is not yet an approved therapy for HES.
- C. False. The *FIP1L1-PDGFR*A associated variant of HES affects men predominantly.
- D. False. The skin is the most frequently affected organ in HES; analysis of current data indicates that cardiovascular complications are the leading cause of death in HES.
- E. True. Given the patient's advanced age and the fact that *Strongyloides* is endemic in parts of rural southeastern United States, he should receive empiric ivermectin while awaiting test results; glucocorticoid treatment should not be delayed given the concern for eosinophilic cardiomyopathy.

Pearls

- HES should be considered in the differential diagnosis in patients with an AEC of >1500 cells/ μ L that has been documented on two different occasions at

least 1 month apart, even if the patient is asymptomatic.

- Risk assessment for *Strongyloides* should be done in patients with HES if corticosteroid is to be given.

Pitfalls

- Diagnosing HES can be challenging because it is a diagnosis of exclusion and can have a variable presentation.
- Management can involve a long-term systemic corticosteroid regimen, and second-line agents should be considered for their steroid-sparing effect.

REFERENCES

1. Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol* 130:607–612.e9, 2012.
2. Crane MM, Chang CM, Kobayashi MG, and Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence. *J Allergy Clin Immunol* 126:179–181, 2010.
3. Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: A multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol* 124:1319–1325.e3, 2009.
4. Roufosse F, and Weller PF. Practical approach to the patient with hypereosinophilia. *J Allergy Clin Immunol* 126:39–44, 2010.
5. Klion AD. How I treat hypereosinophilic syndromes. *Blood* 126:1069–1077, 2015.
6. Yamamoto H, and Khan DA. A 45-year-old man with shortness of breath and eosinophilia. *Allergy Asthma Proc* 37:259–262, 2016.
7. Legrand F, Renneville A, Macintyre E, et al. The spectrum of *FIP1L1-PDGFR*A-associated chronic eosinophilic leukemia: New insights based on a survey of 44 cases. *Medicine (Baltimore)* 92:e1–e9, 2013.
8. Roufosse FE, Kahn JE, Gleich GJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol* 131:461–467.e1–5, 2013.
9. Chusid MJ, Dale DC, West BC, and Wolff SM. The hypereosinophilic syndrome: Analysis of fourteen cases with review of the literature. *Medicine (Baltimore)* 54:1–27, 1975.
10. Lefebvre C, Bletty O, Degoulet P, et al. Prognostic factors of hypereosinophilic syndrome. Study of 40 cases[in French with English abstract]. *Ann Med Interne (Paris)* 140:253–257, 1989. □

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