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Consultation for Elevated Blood Eosinophils: Clinical Presentations, High Value Diagnostic Tests, and Treatment Options

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Abstract

The workup of a patient found to have eosinophilia should follow a thorough path with a detailed history and physical examination aimed at eliciting eosinophilic organ involvement, followed by histological confirmation whenever possible. The differential diagnosis of hypereosinophilia is extensive, but a rational approach beyond the history and physical examination including serologic, blood, and bone marrow cell analyses, genetic testing, and radiologic imaging can distinguish many of the causes. Often input from specialists (eg, hematology, dermatology, pulmonary, gastroenterology, and neurology) can help narrow down the possibilities and eventually result in a specific diagnosis. An accurate diagnosis is key to choosing the optimal treatment for a particular condition, and this is certainly true for eosinophilic disorders. Myeloid neoplasms that present with eosinophilia, for example, may respond to medicines that the allergist may be less accustomed to using, such as immunosuppressive agents and kinase inhibitors. Similarly, newly approved biologics that target IL-5 and eosinophils may provide new options for management. What follows is a case-based approach that helps to underscore key features of diagnosis, management, and follow-up when faced with a patient with a potential eosinophil-related disorder.

Keywords

Eosinophilia; Hypereosinophilic syndromes; Diagnosis; Testing; Treatment

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INITIAL CASE HISTORY

A 42-year-old woman presents for evaluation of an itchy rash and eosinophilia. She was healthy until her mid 30s when she developed arthralgias in her hands and she was diagnosed with sero-negative rheumatoid arthritis. She was treated with nonsteroidal anti-inflammatory drugs with symptomatic improvement. At age 38 years, she developed xerosis and a rash described in previous medical notes as fine, pruritic, erythematous papules involving the extremities and torso without blistering. The rash is persistent, unresponsive to high-potency topical steroids and oral antihistamines, but is improved with oral glucocorticoids. Occasionally, she gets hives on exposure to the cold, and she had a few episodes of localized angioedema. Four years ago, around the time of the development of her skin rash, she was found to have a persistently elevated absolute eosinophil count (AEC) in the 4,000 to 9,000 cells/ μ L range that was partially responsive to high doses of prednisone. Prior eosinophil counts are unavailable, and other blood cell count parameters have been normal. On review of systems she notes profound fatigue and frequent generalized aches and pains.

She was previously evaluated by another allergist, a rheumatologist, a dermatologist, and a hematologist before seeing you. Diagnoses that have been entertained include severe atopic dermatitis, chronic spontaneous urticaria with angioedema, cold urticaria, and hypereosinophilic syndrome (HES). She was first treated with high doses of antihistamines, then with omalizumab with minimal improvement, so these were stopped. She is currently being treated with short courses of prednisone, but skin symptoms promptly return after tapering and she is unhappy about the glucocorticoid side effects including significant weight gain. She denies foreign travel except for a cruise to Mexico and the Caribbean. Her current medications include prednisone 10 mg daily and ibuprofen 600 mg every 6 hours as needed for aches and pains.

On physical examination she has normal vital signs. Head, eyes, ears, nose, and throat, and cardiac, pulmonary, abdominal, and musculoskeletal examination results are normal. Detailed lymph node examination reveals 1-cm mobile, nontender inguinal lymph nodes bilaterally. Skin examination is significant for generalized xerosis and 2 to 5 mm erythematous papules. A faint erythematous rash is noted at the nape of her neck. Physical urticarial testing result is negative. She shows you cellphone pictures demonstrating similar, albeit more intense, diffuse erythematous papules.

Review of outside testing and labs show a recent complete blood cell count (CBC) with differential demonstrating white blood cells 15,200 cells/ μ L, hemoglobin 13.1 g/dL, platelets 198,000/ μ L, and a differential of 28% neutrophils, 16% lymphocytes, 3% monocytes, 52% eosinophils (AEC = 7,850/ μ L), and 1% basophils. A random serum tryptase level was 11 ng/mL, vitamin B₁₂ level was 1,126 pg/mL, and serum total IgE level was 1,320 kU/L. There was no evidence of transaminitis, and glomerular filtration rate was within normal limits. Workup 4 years ago when her AEC was 5,200/ μ L included a skin biopsy demonstrating superficial to deep dermal perivascular lymphocytic infiltrate with scattered eosinophils, and a computed tomography (CT) scan of the chest/abdomen/pelvis was normal. A bone marrow biopsy and aspirate showed trilineage hematopoiesis with an

increase in morphologically normal eosinophils, no increase in mast cell aggregates, and only few scattered spindle-shaped mast cells by tryptase immunohistochemical staining. Testing for both the *JAK2 V617F* and the *FIPIL1-PDGFR* mutation by fluorescence *in situ* hybridization (FISH) was negative and T-cell receptor gene rearrangement by RT-PCR analysis revealed an oligoclonal pattern.

INITIAL DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hypereosinophilia is quite broad. Important historical details that are gathered in the initial workup include determination of the onset, duration, and magnitude of the eosinophilia as well as associated symptoms, taking into consideration the types and doses of medications taken when the counts were obtained. Although symptoms can occur with even mild eosinophilia in a patient with HES, for the purposes of the initial workup, characterization of marked eosinophilia ($>5000/\mu\text{L}$) as well as the duration is important because it might alter the decision to initiate treatment more urgently.¹ Other important historical factors include consideration of exposures such as recent infections or medications. An appropriate exposure history should include determination of recent or remote travel to, or history of residence in, areas with parasitic infestations as well as other exposure history that might coincide with eosinophilia. Depending on the acuity and duration of eosinophilia, as well as types of organs involved, certain parasitic infections are more commonly the cause of eosinophilia when presenting in North America. For example, *coccidioides* species, *echinococcus*, and *fasciola* species typically present with acute eosinophilia and may be seen in clinical practice in North America. In contrast, common causes of chronic eosinophilia include *Strongyloides stercoralis*, *clonorchis*, *ospisthorchis* species, and *Paragonimus* species. Some species such as *Schistosoma* and *Trichinella* may present with either acute or chronic eosinophilia. Residence or travel to geographic locations with parasite exposure and the types of organs involved should guide the testing for individual parasitic infection. The most appropriate testing for suspected parasitic infections is comprehensively reviewed elsewhere.² Although patients with HIV or tuberculosis may have incidentally noted hypereosinophilia, neither of these infections typically present with eosinophil-mediated disease, though a judicious workup should consider these in the differential diagnosis of laboratory findings of eosinophilia. Finally, a historical presence of severe, invasive, or unusual infections, especially in pediatric patients, should raise a concern for and consideration of workup for immunodeficiency-related causes of eosinophilia.³ Medication exposures should be addressed, including initiation and duration of taking over-the-counter or prescription medications, because eosinophilia may occur after medication exposure. Hypersensitivity reactions (with rash and/or renal injury being most common) occur in 25% of those who develop eosinophilia after exposure to antibiotics such as vancomycin, penicillins, rifampin, or linezolid.⁴ For patients who present with eosinophilia, respiratory symptoms, or pulmonary infiltrates after drug exposure, acute eosinophilic pneumonia is a possibility. The most common drugs causing acute eosinophilic pneumonia include daptomycin, minocycline, nitrofurantoin, mesalamine, and sulfasalazine.⁵ Drug rash with eosinophilia and system symptoms (DRESS) is a less common reaction after medication exposure and is characterized by the development of eosinophilia and systemic symptoms (including liver injury) 2 to 8 weeks after initiation of causative medications such

as aromatic antiepileptic drugs (eg, carbamazepine), allopurinol, sulfa-containing medications, and antibiotics.⁶ Systemic symptoms such as fevers, night sweats, and weight loss may suggest malignancy (eg, lymphoma and leukemia). Finally, autoimmune conditions (eg, rheumatoid arthritis, IgG4-related disease, systemic lupus erythematosus, and eosinophilic myositis; see Table I) are also in the differential diagnosis of peripheral eosinophilia.^{7,8}

PHYSICAL EXAMINATION

In the absence of an obvious trigger for eosinophilia, the ensuing physical examination should be targeted at the presenting symptoms and suspected organ involvement but at a minimum should include assessment of possible upper and lower airway involvement including chronic rhinosinusitis with or without nasal polyposis, assessment of mucosal surfaces for ulcers, dermatologic assessment focused on rashes, nail beds, lymph node examination, pulmonary and cardiac examination, musculoskeletal examination, assessment for hepatosplenomegaly, and neurologic examination for focal findings as well as assessment for neuropathy.

INITIAL DIAGNOSTIC TESTING

Routine testing (Figure 1 and Table II) should include a CBC with differential, assessment of liver and kidney function, an electrocardiogram, pulmonary function tests, troponin, and echocardiogram (followed by cardiac magnetic resonance imaging [MRI] if cardiac involvement is suspected). CT scans of the chest, abdomen, and pelvis are performed as part of the assessment of adenopathy, organomegaly, masses, or other organ infiltration. Testing for pertinent parasitic infections via serology or stool examination should be performed or the patient should be referred to an infectious diseases specialist for further workup if a suspicious travel history is obtained.

SUBSEQUENT TESTING FOR HES

In patients for whom other disorders have been ruled out and the working diagnosis is HES, but treatment is not urgent, additional testing (Table II) should include microscopic examination of a peripheral smear to look for dysplastic eosinophils, plus assessment for elevations in random serum tryptase and vitamin B₁₂ levels (elevations found more often in myeloid HES).⁹ Consideration of biopsies to determine the presence of tissue eosinophilia and specific organ involvement should be considered on the basis of clinical picture. In cases in which lymphadenopathy is present, an excisional lymph node biopsy should be considered.

Although some patients may be entirely asymptomatic and present with hypereosinophilia of uncertain significance, adequate, and iterative, testing is essential to ensure no organ-system involvement develops during follow-up off treatment.¹⁰ Some patients are deemed to have “overlap HES,” a term used when the clinical picture of a discrete diagnosis overlaps with that of HES. Once other diagnoses have been ruled out, additional testing that might help with characterization of the subtype of HES includes T-cell clonality by RT-PCR and flow

cytometry for assessing aberrant T cells, as seen in lymphoid hyper-eosinophilic syndrome (LHES). Genetic testing of a peripheral blood sample should be performed routinely in those with a myeloid presentation. These should include tests for an interstitial deletion resulting in *FIPIL1-PDGFR* gene rearrangement (by FISH or RT-PCR, the latter sometimes being positive even when FISH testing is negative¹¹) and for *JAK2* mutations (by RT-PCR). Additional testing for mutations found in association with hypereosinophilia, for example, *PDGFRB*, *FGFR1*, and *CKIT D816V*, is in general best performed on a bone marrow sample because of enhanced sensitivity.

BONE MARROW EXAMINATION: TO DO OR NOT TO DO

A common question is when to pursue a bone marrow biopsy and aspirate with cytogenetics. In patients for whom HES is suspected, we advise a hematology consult with bone marrow biopsy for the following situations: (1) If the patient has 1 or more signs of a myeloid disorder including elevated serum vitamin B₁₂ or random serum tryptase, dysplastic or abnormal-appearing eosinophils in a peripheral smear, organomegaly, or a steroid-refractory presentation; (2) if the patient has persistent marked hypereosinophilia, an abnormal T-cell immunophenotype by flow cytometry, elevated lactate dehydrogenase, abnormalities of other cell lineages (eg, concomitant anemia and thrombocytopenia), T- or B-cell clonality by PCR, to rule out malignant presentations of HES, or (3) when considering treatment with immunosuppressive or cytotoxic agents.

NEXT STEPS

You first determine that a *Strongyloides* serology is appropriate considering the history of hives, edema, and respiratory complaints. You send serology for anti-cyclic citrullinated peptide as you question the rheumatoid arthritis diagnosis and schedule a repeat echocardiogram and recheck serum troponin levels. *Strongyloides* serology and anti-cyclic citrullinated peptide come back negative, and troponin is below the level of detection. You ask her to withhold nonsteroidal anti-inflammatory drugs for 4 weeks to ensure the hives and angioedema are not related to intermittent use of these agents. The echocardiogram will be done in 2 weeks. You diagnose the patient provisionally with HES on the basis of skin and soft tissue involvement, and constitutional and musculoskeletal symptoms.

At this point, her case could evolve in multiple different directions. To underscore how the clinical picture and disease progression plays a critical role in developing a definitive diagnosis, the remainder of this review has been written in a style reminiscent of the “Choose your own adventure” books by describing how to workup specific disease features of subtypes of HES, how diagnosis of various subtypes of HES might influence treatment choices,¹² and suggesting optimal monitoring of such patients.

Cough, Wheeze, and Anosmia

Two months after her initial visit with you, she describes worsening daily wheezing, a nonproductive persistent cough especially at night, nasal congestion, and new onset of shortness of breath when exercising. You see her as an outpatient, and despite no previous diagnosis of asthma, this is confirmed by physical examination and pulmonary function

testing, showing a moderate obstructive airflow limitation with significant improvement following inhaled bronchodilator administration. You start her on a combination inhaler containing a corticosteroid and long-acting bronchodilator, and provide a short-acting inhaled bronchodilator for rescue use. A chest x-ray is normal. One month later she is much improved, but now mentions that she has lost her sense of taste and smell. Examination confirms the presence of nasal polyposis. She has no reaction when taking aspirin or ibuprofen PRN, as recently as last week. Repeat CBC is normal other than her AEC, which remains elevated at 3,300/ μ L. Testing for antinuclear cytoplasmic antibodies is negative. You start a 1-week course of prednisone without taper followed by daily use of an intranasal steroid, and her sense of smell and taste improve. At her next visit 2 months later, her nasal congestion is worsening although her asthma is stable, but she now mentions numbness and tingling in her left leg distally, as well as abdominal bloating and nausea. Neurologic examination suggests weakness and foot drop. You refer her to a neurologist, a rheumatologist, and a gastroenterologist urgently who make the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) on the basis of an abnormal electromyography and nerve conduction studies followed by peroneal nerve biopsy demonstrating perivascular eosinophils and vasculitis. Her esophagogastroduodenoscopy shows more than 60 eosinophils/hpf in the antral mucosa, and 1 g of methylprednisolone is given intravenously (IV) for 3 days¹³ while she decides whether or not to agree to the rheumatologist-recommended immunosuppressive therapy. Please go to the “Treatment, Follow-up, and Management” section for discussion of agents to use in variants of HES with predominantly respiratory involvement.

Cardiac and Thromboembolic Complications

The patient calls you crying after her echocardiogram showed “a problem” with one of her valves. She has been having dizziness, “trouble seeing” very well, and feels weak. You send her to the emergency room where a CBC with differential shows white blood cells 15,900 cells/ μ L, hemoglobin 8.9 g/dL, mean corpuscular volume 99 fL, AEC 7,484/ μ L, platelets 129,000/ μ L, and normal chemistries. The emergency department physician notes splenomegaly and diminished strength in her right upper extremity and they activate the stroke protocol. CT scan of the head is unrevealing, but MRI demonstrates punctate areas of infarction in the posterior middle cerebral artery territory. She is admitted and is started on heparin and methylprednisolone IV; hematology, cardiology, and neurology services are consulted. An echocardiogram demonstrates thickening and reduced motility of the posterior mitral valve leaflet. Her AEC is now lower at 1,100/ μ L and 1 g of methylprednisolone IV is administered. The hematologist schedules a repeat bone marrow biopsy and additional workup. The cardiologist schedules a cardiac MRI on discharge and adds a beta-blocker. The hospitalist calls you to give you an update and to get advice on treating the eosinophilia because her AEC is not as responsive to glucocorticoids as expected.¹⁴ Because the counts have improved, you advise using the results of the bone marrow biopsy, cytogenetics, and flow cytometry that was sent to guide therapeutic decisions. The results will be available the next day so you finish up your clinic schedule and plan to stop by the hospital to see her quickly before you head home for the day. Proceed to the myeloid presentations of HES in the “Treatment, Follow-up, and Management” section for further discussion of treatment of myeloid HES and myeloid neoplasms presenting with eosinophilia.

Worsening Rash and Pruritus

The patient calls to follow-up on her echocardiogram results and is relieved they are normal. While on the phone she mentions that her itching and skin issues have worsened. She describes “looking red all over.” Initially she attributed this to sitting in a hot tub at the gym for too long, but the redness has not resolved a week later, and if anything, is worsening despite the application of topical steroids. The diphenhydramine she found in her medicine cabinet has not helped the redness or the itching and she has trouble sleeping due to the pruritus. She also mentions before hanging up that she has a “large lump” in her groin that is new. You schedule her for an urgent visit the next morning.

Upon evaluation the patient is found to have a firm, non-tender 3-cm inguinal lymph node, along with generalized erythroderma with significant scaling and well-demarcated red, macular lesions and raised nodules on her legs. Her oral mucosa and eyes are unaffected. You contact your dermatology colleague for an urgent consult and biopsy. Two skin biopsies are performed: one on an area spared from topical steroid application on the upper back, and one of the well-demarcated lesions on her lower extremities. The dermatologist now suspects cutaneous T-cell lymphoma. The patient is worried, but you reassure her that although development of hematologic malignancy in patients with eosinophilia is rare,¹⁵ causes such as solid-organ tumors¹⁶ or hematologic malignancies such as lymphoma¹⁷ do need to be ruled out. You discuss that this might be an inflammatory or infectious worsening of her atopic skin disease, or a lymphoid variant of HES (LHES). A drug reaction-induced erythroderma is unlikely after review of her over-the-counter and prescribed medication list.¹⁸ Although she did not have an abnormal T-cell immunophenotype 2 years ago, flow cytometry and T-cell receptor rearrangement studies should be repeated. You advise that the enlarged lymph node be removed and analyzed to rule out a malignant process. You send her for a CBC with differential, a manual blood-smear to look for Sézary cells or other abnormalities, a CT scan of the chest, abdomen, and pelvis, repeat flow cytometry to look for any abnormal T- or B-cell populations (eg, CD3⁺CD4⁺ or other aberrant T cells that may be present in LHES),^{19,20} and T- and B-cell rearrangement studies. You advise that treatment of the underlying disorder is the best approach for obtaining symptom relief of skin manifestations and this testing will help guide treatment. She asks what treatment would be used if she has LHES rather than a malignancy. Skip to the section on treatment of lymphoid HES for a discussion of agents commonly used in LHES.

TREATMENT OPTIONS, FOLLOW-UP, AND MANAGEMENT

Subtypes of HES with predominantly airway or pulmonary involvement

You explain to the patient that asthma with an eosinophilic phenotype could be one of several diseases. In the setting of significant peripheral eosinophilia, EGPA (with or without eosinophilic pneumonia), aspirin-exacerbated respiratory disease, and allergic bronchopulmonary aspergillosis are often difficult to distinguish on first presentation. Some disorders such as EGPA or eosinophilic pneumonia may be considered “overlap HES” as are other organ-restricted eosinophilic involvements (eg, eosinophilic pneumonia or eosinophilic gastrointestinal diseases). Additional testing, such as serum IgE levels, specific IgE and precipitating antibodies to *Aspergillus fumigatus*, chest and sinus imaging, and assessment

for other organ involvement, can help narrow down the possibilities. In her case, progression of her disease beyond the airways suggests that this is a multisystem disorder that will require systemic glucocorticoid therapy. Although glucocorticoids are the initial drug of choice for “overlap HESs” (Figure 1), individual overlap HES syndromes may respond to specific treatments, such as the use of food avoidance diets or swallowed topical glucocorticoids for eosinophilic gastrointestinal disorders that might be advised in addition to other therapies. She seems upset by the notion that she will need glucocorticoids long-term and you discuss the availability of biologics that target IL-5 (mepolizumab, reslizumab) or its receptor (benralizumab), which have been a welcome recent addition to the treatment armamentarium for asthma, some of which are in clinical trials for HES and eosinophilic gastrointestinal disorders currently. All 3 of these drugs have been shown to reduce asthma exacerbations and have oral glucocorticoid-sparing activity,²¹ and although none of these are approved by the Food and Drug Administration (FDA) for HES to date, preliminary data suggest efficacy in HES^{22–24} for mepolizumab, and additional clinical trials are underway. Mepolizumab is approved for EGPA at the 300-mg dose and nasal polyposis seen in EGPA may also respond to therapy.²⁵ You discuss the fact that although dupilumab, which targets the IL-4 receptor α chain, is approved for the treatment of moderate to severe atopic dermatitis,²⁶ and is being studied as a treatment for asthma,²⁷ and nasal polyposis,²⁸ it has not been studied for use in EGPA.²⁹ Finally, you mention that an oral drug called dexamipexole is showing promise in reducing eosinophils in some patients with HES but is still undergoing clinical trials testing and thus is not yet FDA approved.³⁰

She elects not to pursue cyclophosphamide because of concerns regarding side effects.^{31,32} Despite a slow taper of prednisone, she is unable to be maintained on less than 20 mg daily without flare of her paresthesias or gastrointestinal symptoms. Her rheumatologist suggests rituximab³³ but you suggest mepolizumab 300 mg instead, which she starts subcutaneously every 4 weeks,³⁴ and prednisone is tapered to 5 mg every other day over 2 months with maintained disease control. You reiterate the importance of monitoring and prevention of known glucocorticoid side effects such as osteoporosis by assessing 25-hydroxy vitamin D levels, bone densitometry annually, and supplementation with calcium and vitamin D.³⁵ You recommend yearly eye examinations with dilation to permit a thorough retinal examination, and monitoring of blood glucose levels periodically to screen for diabetes. You suggest she may attempt to wean oral prednisone completely, with monitoring of signs and symptoms of disease recurrence, along with peripheral blood eosinophil counts, every 6 to 12 months if all other aspects of her disease remain stable, because some patients with EGPA have complete remission.³²

Myeloid presentations of HES

You see the patient in follow-up after discharge from the hospital. The bone marrow results revealed a hypocellular marrow, with trilineage hematopoiesis. Red blood cells and platelets were less than normal on the aspirate smear. There were no blasts or dysplastic eosinophils, but cytogenetics revealed a 5q deletion abnormality. You review her bone marrow biopsy from 2 years ago and realize that cytogenetics were not performed. Fortunately, she does not have neurologic findings, and you tell her that she will need close follow-up after initiation of therapy and a repeat bone marrow biopsy after treatment to ensure improvement. Her

cardiac MRI showed delayed global enhancement of the endomyocardium on T2-weighted images as well as a small left ventricular thrombus. She is therapeutic on Warfarin. Her husband asks about treatment with imatinib after scouring the HES patient listserv. You respond that although imatinib is the only FDA-approved agent for HES, many agents are used off-label in clinical practice, and the approach to myeloid disorders in general depends on the mutation, if known. For example, *PDGFRA* or *PDGFRB* are extraordinarily responsive to imatinib³⁶; however, myeloid HES with unknown mutations have variable responses to imatinib but enough patients respond to warrant a trial.³⁷ Some myeloid neoplasms with clonal eosinophilia, such as *ETV6-FLT3*,³⁸ are imatinib-resistant but may respond to multitargeted tyrosine kinase inhibitors, whereas others (eg, *PCMI-JAK2* rearrangements or *FGFR1* mutations³⁹) are resistant to imatinib and are treated with *JAK* inhibitors⁴⁰ or stem cell transplantation.⁴¹ Patients with HES mutations in 5q have been treated with lenolidomide, similar to patients with myelodysplastic syndrome (MDS) and 5q syndrome⁴² but the hematologist would be the one to decide on appropriate treatment. You advise a follow-up cardiac MRI in 3 months to assess resolution of the thrombus, especially because it was not detected on the echocardiogram. They ask how long she will need anticoagulation, but unfortunately there are no evidence-based guidelines on the optimal duration of therapy, so you discuss revisiting this issue if and when disease remission occurs.

Lymphoid variant HES

The patient returns for follow-up of her results. You inform her that the biopsies were not suggestive of malignancy, and her CT scan was unrevealing, but that her T-cell receptor rearrangement studies and flow cytometry were suggestive of lymphoid HES. Although the itching has been relatively well controlled after increasing prednisone to 20 mg daily and using hydroxyzine 25 to 50 mg 3 to 4 times daily, she is worried about return of symptoms with tapering. You review appropriate skin care including advising warm-water baths rather than hot-tub use and daily use of “soak-smear” with application of topical corticosteroids and emollients.⁴³ You discuss that treatments for HES subtypes vary, and patients with LHES often require higher prednisone doses.¹⁴ As such, although not specifically approved for HES, second-line therapies such as IFN- α ,⁴⁴ or other immunosuppressive agents targeting T cells (eg, mycophenolate mofetil,⁴⁵ cyclosporine,⁴⁶ and methotrexate⁴⁷) can be tried. Mepolizumab was administered at a dose of 750 mg IV every 4 weeks in a large trial of subjects with HES and subjects with LHES demonstrated a similar response to therapy as did other subtypes of HES, but antiIL-5 therapies are not approved for HES.^{23,48} In some cases, regression of the clone with treatment has been associated with clinical improvement.⁴⁹ Finally, new JAK kinase inhibitors such as ruxolitinib and tofacitinib have been used in small numbers of patients with promising results⁵⁰ but are not approved for use in HES and are being evaluated for treatment efficacy in small studies. Despite the listed side effects, the patient elects to start IFN- α (2A or 2B) because of its track record of efficacy in LHES.⁵¹ You discuss the side-effect profile including treatment-limiting side effects such as severe depression or psychosis, flu-like symptoms on treatment initiation or with dose-increases, development or exacerbation of autoimmune phenomena (eg, autoimmune thyroiditis), ocular side effects, and commonly fatigue or cognitive side effects. A lower daily subcutaneous dose is sometimes better tolerated and can later be switched to a weekly pegylated form, and/or sometimes the dose can be reduced if the medication is effective and

tolerated. You check baseline labs including a fasting lipid profile and give her a prescription for periodic monitoring of CBC with differential, liver function tests, chemistries including electrolytes, and thyroid stimulating hormone level. She had an appointment with an ophthalmologist 2 weeks ago, but you advise continued annual examinations and for new ocular symptoms. You tell her that you will be monitoring her clonal population at least twice a year and sooner if she develops new symptoms because some patients with LHES may develop lymphoma.^{19,52}

CONCLUSIONS

This review has provided various scenarios within case presentations to illustrate crucial findings and decision points that allow the physician to distinguish HES from other causes of eosinophilia (Table I). The cases help the clinician classify the type of HES by obtaining a detailed history and physical examination (Figure 1), and by incorporating the results of select tests (Table II) to help guide the diagnosis. As the workup evolves, it may be necessary to enlist the help of other specialists, for instance, consultation with hematology for bone marrow testing. Making the diagnosis of HES, including the subtype of lymphocytic, myeloid, idiopathic, or another overlap form of HES such as EGPA, then helps to dictate treatment options, which may vary among forms of HES. The optimal first- or second-line treatment (Figure 1), prognosis, and monitoring for complications of disease and treatment-related side effects are also unique to each subtype of HES. Although HES is a rare disease, it is hoped that with an increased focus on mechanisms of disease pathogenesis and biomarker discovery, that personalized approaches to treatment will lead to improved outcomes and safer treatments for such patients.

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Abbreviations used

AEC	Absolute eosinophil count
CBC	Complete blood cell count
CT	Computed tomography
EGPA	Eosinophilic granulomatosis with polyangiitis
FDA	Food and Drug Administration
HES	Hypereosinophilic syndrome
IV	Intravenously
LHES	Lymphoid hypereosinophilic syndrome

MRI

Magnetic resonance imaging

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Learning objectives:

1. To initiate a rational and cost-effective workup for eosinophilia based on clinical and laboratory features at presentation.
2. To formulate a differential diagnosis and initiate appropriate treatments for patients with specific causes of eosinophilia.
3. To understand how to monitor and assess treatment responses in patients with eosinophilia.

FIGURE 1.

Algorithm for the initial and subsequent workup of persistent hypereosinophilia as well as treatments for various subtypes of HES. Because the differential diagnosis for hypereosinophilia is very broad, what is shown is a thorough progression, including historical, physical examination, and laboratory testing, from an initial (1), and subsequent (2) workup to more specialized testing (3) that should result (yellow arrows) in either a diagnosis of a specific HES subtype or an alternate diagnosis. For certain diagnoses, treatment might need to be instituted urgently (orange box) before further workup (3) can proceed. If HES is suspected, the ultimate goal is to determine the exact HES subtype so that optimal treatment can be implemented (Box: Treatment by subtype). Examples of medications are listed for each form of HES including agents that may be used for disease control and/or steroid-sparing activity. *EMG/NCV*, Electromyography/Nerve Conduction Velocity study; *HE_{us}*, hypereosinophilia of unknown significance; *LDH*, lactate dehydrogenase; *ECG*, electrocardiogram; *EGID*, eosinophilic gastrointestinal disorder; *TKI*, tyrosine kinase inhibitor. *Many agents used to treat HES are used off-label but are considered standard of care, such as hydroxyurea and IFN- α . Others listed here, such as antieosinophil biologics (mepolizumab, reslizumab, and benralizumab) and oral JAK inhibitors are FDA approved but not for the treatment of HES, although there are published data regarding potential beneficial effects when used off-label for HES (see text). Ongoing trials in HES with these and other agents should shed additional light on their safety and efficacy.

TABLE I.

A nonexhaustive list of autoimmune, dermatologic, and gastrointestinal disorders that can present with varying degrees of blood or tissue eosinophilia

Differential diagnosis	Peripheral eosinophilia	Tissue eosinophilia or evidence of eosinophil granule protein deposition
Autoimmune disease		
IgG ₄ -related disease	+/-	+
EGPA (MPO/PR3+ or -)	++	++
Eosinophilic myocarditis	Rarely	+
Bullous pemphigoid	+	+
Eosinophilic myositis (and subtypes)	+/-	+
Sarcoidosis	+/-	+
Primary biliary cirrhosis	+/-	+
Rheumatoid arthritis	Rarely	+/-
Dermatologic conditions		
Eosinophilic fasciitis	+/-	+
Eosinophilic cellulitis (Well's)	+/-	+
Gastrointestinal conditions		
Eosinophilic esophagitis	+/-	++
Eosinophilic gastritis	++	++
Eosinophilic colitis	+	++

+/-, May or may not be present; +, usually present; ++, present high numbers;

MPO, myeloperoxidase; *PR3*, proteinase-3.

TABLE II.

Abnormal test results obtained during the workup of HES that can help specify disease subtype

Test	MHES	LHES	Idiopathic HES	Overlap HES	Other causes*
CBC with differential					
Eosinophilia	+	+	+	+	+
Anemia, thrombocytopenia	+			+	[‡]
Dysplastic eosinophils	+				
Elevated transaminases			+	+	[§]
Elevated serum LDH	+	+/-			[‡]
Abnormal renal function and urine test results				+	[§]
Elevated serum tryptase and vitamin B ₁₂	+				+
Aberrant T-cell immunophenotyping by flow cytometry		+			+
T-cell clonality by RT-PCR		+			+
CT scan					
Sinus disease			+	+	+
Abnormal chest, abdomen, and pelvis imaging			+	+	+
Serum ANCA-positive (MPO/PR3)	+	+		+	[§]
Troponin, electrocardiogram, and echocardiogram abnormalities	+	+	+	+	+
Biopsy of involved tissue	+	+	+	+	+
Bone marrow genetics mutations	+	+	+		

ANCA, Antinuclear cytoplasmic antibody; LDH, lactate dehydrogenase; MHES, myeloid HES; MPO, myeloperoxidase; PR3, proteinase-3.

* These include drug hypersensitivity, autoimmunity, infection, malignancy, and others, and might necessitate additional testing not listed here.

[‡] May be present in eosinophilic gastrointestinal disorders overlapping with HES.

[‡] Hematologic abnormalities may be present in some autoimmune conditions and malignancy.

[§] May be present in EGPA or EGPA-overlap HES

^{||} These include molecular testing for mutations in PDGFRA, PDGFRB, FGFR1, JAK2, and CKIT D816V.