

## Challenging Clinical Cases

# Hypereosinophilic syndrome presenting acutely with neurologic signs



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**A 70-year-old white man with a longstanding history of allergic rhinitis and nasal polyposis and a relatively recent onset of chronic cough 1 year earlier presented to the hospital for a 1-week duration of neurologic symptoms, including chronic and worsening neck pain, bilateral upper extremity weakness, difficulty gripping objects, blurry vision, confusion, change in gait, and difficulty with initiation of urination. His medical history also included essential hypertension, dyslipidemia, gastroesophageal reflux, and shingles. On the basis of his initial neurologic examination, which revealed dysmetria, bradykinesia, intention tremor, and wide-based gait, a lumbar puncture and brain magnetic resonance imaging (MRI) were ordered to look for evidence of movement disorder, infectious process, or multiple sclerosis. Cerebrospinal fluid revealed a normal blood cell count with an elevated protein level and tested negative for infectious causes. Initial brain MRI revealed evidence of numerous small supratentorial and infratentorial acute to subacute infarcts predominantly in the watershed distribution. Cervical spine MRI did not reveal any significant findings. Incidentally, the patient's complete blood cell count revealed an eosinophil count of 8100 cells/mm<sup>3</sup> and total IgE level of 729 IU/mL. At this point, the allergy, hematology, and rheumatology departments were consulted to evaluate for causes of eosinophilia.**

Eosinophilic contribution to disease encompasses a broad spectrum of pathologic conditions from allergic rhinitis and T<sub>H</sub>2 predominant asthma, allergic bronchopulmonary mycoses, allergic fungal sinusitis, and vasculitis to organ-specific eosinophilic disease, including eosinophilic pneumonia, and systemic

hypereosinophilic syndrome (HES) with involvement of the blood in addition to any end-organ involvement.

Eosinophils are white blood cells from granulocytic lineage originating in the bone marrow and migrating to the blood, where they account for 1% to 6% of leukocytes. Influence from the cytokines granulocyte-macrophage colony-stimulating factor, interleukin (IL) 3, and IL-5 promote eosinophil maturation from myeloid precursors. Their half-life is limited to 8 to 18 hours in the blood but is prolonged by autocrine production of granulocyte-macrophage colony-stimulating factor to several weeks in the tissues where they typically reside.<sup>1,2</sup> Historically, eosinophils have been described as effector cells in innate immunity. They are honed to the peripheral tissues, including spleen, lymph nodes, thymus, and the submucosal linings of the gastrointestinal, respiratory, and genitourinary tracts, by eotaxins in response to allergens in atopic disease and as host defense against parasitic disease.<sup>3,4</sup> With further study of the eosinophil, additional functions have been identified, including host protection against bacterial, viral, and fungal infection, tissue remodeling, allograft rejection, and tumor surveillance.<sup>3,5,6</sup> The eosinophil also contributes to pathologic states, such as those seen in idiopathic eosinophilic diseases.<sup>7</sup> Once in the tissues, cell degranulation releases proinflammatory cationic protein mediators intended to eliminate host threat, which then may cause bystander tissue damage, further perpetuating the disease process.

Eosinophilia is defined as an absolute eosinophil count (AEC) of 450 to 500 cells/mm<sup>3</sup> or more of blood. It has been further categorized as mild (AEC ≥450–1500 cells/mm<sup>3</sup>), moderate (AEC ≥1,500–5,000 cells/mm<sup>3</sup>), and severe (AEC ≥5,000 cells/mm<sup>3</sup>), with the term *hypereosinophilia* reserved for moderate and severe levels with an AEC of 1,500 cells/mm<sup>3</sup> of blood or more<sup>8,9</sup> (Table 1). The chronicity of the eosinophilia must also be defined as transient, episodic, or chronic. From there, investigation into hypereosinophilia should be pursued if the patient's eosinophilia is moderate or severe and persistent (Fig 1).

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**Table 1**  
Severity of Peripheral Blood Eosinophilia

| Eosinophil level | Eosinophil count, cells/mm <sup>3</sup> |
|------------------|-----------------------------------------|
| Mild             | 500–1,500                               |
| Moderate         | >1,500                                  |
| Severe           | >5,000                                  |

Some factors, including fever, bacterial or viral infection, and systemic glucocorticoid administration, may decrease eosinophil numbers, potentially masking significantly elevated values. In addition, some conditions may perpetuate with a localized tissue eosinophilia, absent of peripheral blood eosinophilia. Further examination of sputum, nasal secretions, or tissue biopsy may be needed to determine localized organ-specific eosinophilia.

On record review, it was discovered that the patient's eosinophil count had been 2,310 cells/mm<sup>3</sup> and the total IgE level was 369 IU/mL before starting omalizumab treatment more than 2 months earlier. This qualifies as prolonged moderate to severe eosinophilia. Reviewing his atopic history revealed that his rhinitis had been treated with immunotherapy injections for 30 years, and he had bilateral maxillary sinusotomy and total ethmoidectomy and polyp resection 2 years earlier. Polyposis and sinusitis were controlled with intranasal steroid spray. His relatively recent onset of chronic productive cough was diagnosed as asthma with a severely obstructive pulmonary function test without evidence of bronchodilator reversibility several months before his presentation. He did not experience symptoms of wheeze, chest pain, shortness of breath, fevers, night sweats, weight loss, or lymphadenopathy. His respiratory symptoms were refractory to inhaled corticosteroid therapy, inhaled corticosteroid and long-acting  $\beta$ -agonist combination therapy, and

leukotriene receptor antagonist therapy. He started treatment with omalizumab, 300 mg every 2 weeks, the month before admission, and he had received 2 doses with some improvement in cough. He had been receiving multiple courses of oral corticosteroids, with his greatest resolution of symptoms from this therapy. Review of systems was also positive for intermittent facial rash, arthralgias to upper and lower extremities, and general fatigue. Pertinent family history was positive for asthma in his mother and leukemia in his father. He denied smoking history or environmental exposures.

New-onset asthma in a 70-year-old man is unusual, and his respiratory symptoms were initially thought to be likely because of some other cause, especially in the setting of hypereosinophilia. Respiratory disorders associated with eosinophilia include eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic pneumonia, allergic bronchopulmonary aspergillosis (ABPA), tuberculosis, parasitic infection, drug-induced reaction, autoimmune process, malignant tumor, and HES with end-organ lung involvement. Atopic disease may also increase eosinophil levels however not to the degree seen in this patient on admission. This differential diagnosis of eosinophilia is broad; therefore, a detailed history and a focused clinical workup are needed to reach an appropriate diagnosis.

In 2011, revised guidelines were issued by members of the Working Conference on Eosinophil Disorders and Syndromes, which outlined an approach to classification and organization of eosinophilic disorders. These definitions then require subclassifications as the clinician considers the broad differential diagnosis (Table 2) that guides diagnostic workup.

Sustained peripheral blood eosinophilia in excess of an eosinophil count of 1,500 cells/mm<sup>3</sup> on 2 separate occasions at least 4 weeks apart without an apparent cause or pathologic confirmation of tissue hypereosinophilia should prompt consideration of

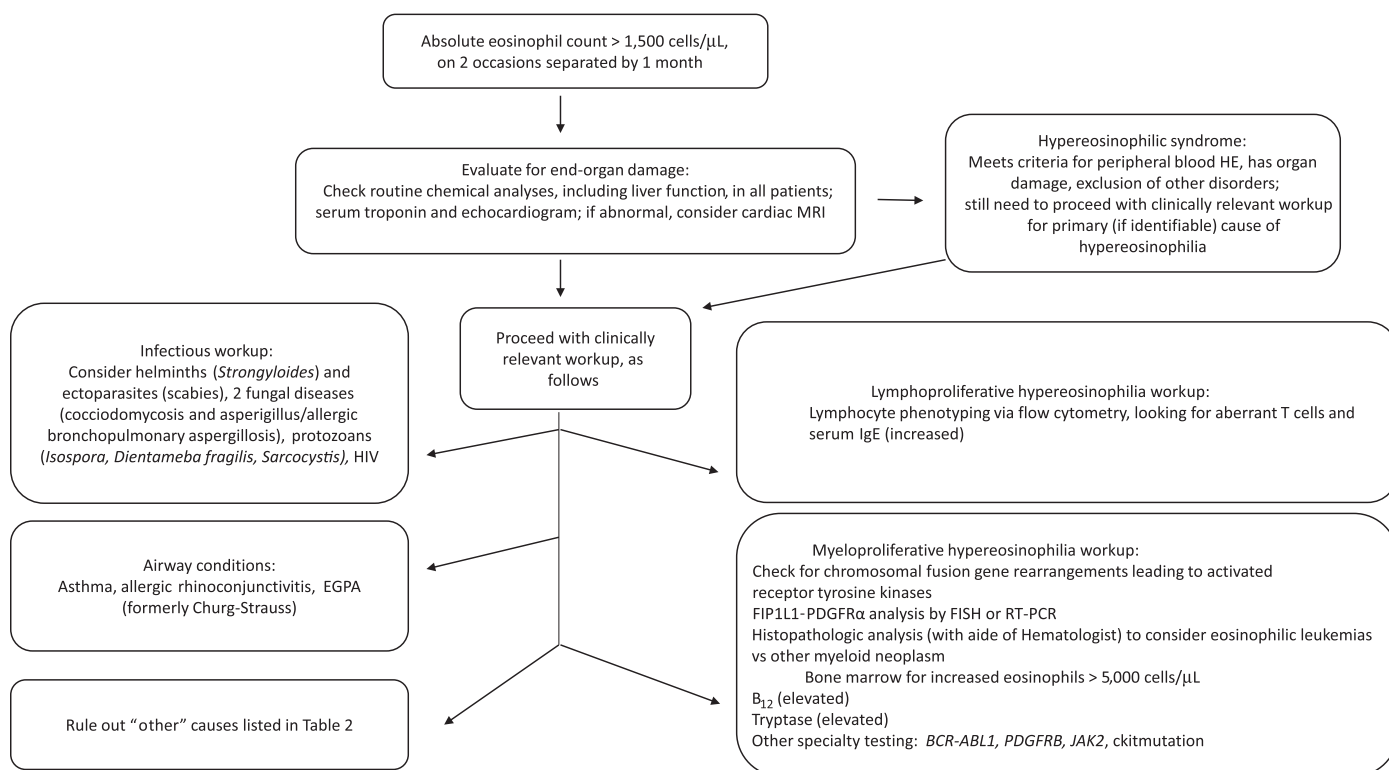


**Figure 1.** Decision tree for hypereosinophilia. Beginning with verifying the persistent elevation of the eosinophil count, move through the decision tree in a clinically relevant workup for the patient. EGPA indicates eosinophilic granulomatosis with polyangiitis; FISH, fluorescence in situ hybridization; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RT-PCR, reverse-transcription polymerase chain reaction.

**Table 2**  
Classifications of HESs and Other Causes of Eosinophilia<sup>a</sup>

| HESs (6 clinical variants)                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| M-HES:                                                                                                                                                                                                                                                                        |
| M-HES: no clonality                                                                                                                                                                                                                                                           |
| Chronic eosinophilic leukemia: <i>FIP1L1/PDGFR</i> A-positive CEL                                                                                                                                                                                                             |
| L-HES (secondary/reactive):                                                                                                                                                                                                                                                   |
| Nonclonal T cells                                                                                                                                                                                                                                                             |
| Clonal T cells                                                                                                                                                                                                                                                                |
| Episodic angioedema with eosinophilia (Gleich syndrome) (many with clonal T cells)                                                                                                                                                                                            |
| Undefined                                                                                                                                                                                                                                                                     |
| Benign with no symptoms or organ involvement                                                                                                                                                                                                                                  |
| Symptomatic without features of M-HES or L-HES                                                                                                                                                                                                                                |
| Familial: unknown mechanism                                                                                                                                                                                                                                                   |
| Overlap: organ-restricted eosinophilia                                                                                                                                                                                                                                        |
| Associated: eosinophilia in the setting of a known diagnosis, such as EGPA                                                                                                                                                                                                    |
| Other causes of eosinophilia                                                                                                                                                                                                                                                  |
| Infections                                                                                                                                                                                                                                                                    |
| • Helminths ( <i>Strongyloides</i> ) and ectoparasites (scabies), 2 fungal diseases (coccidiomycosis and <i>Aspergillus</i> /ABPA), protozoans ( <i>Isospora</i> , <i>Dientameba fragilis</i> , <i>Sarcocystis</i> ; <i>Giardia</i> does NOT), HIV                            |
| Airway diseases with eosinophilia                                                                                                                                                                                                                                             |
| • Asthma, allergic rhinoconjunctivitis, EGPA (formerly Churg-Strauss)                                                                                                                                                                                                         |
| Other                                                                                                                                                                                                                                                                         |
| • Pulmonary syndromes: Loeffler syndrome ( <i>Ascaris</i> ), chronic eosinophilic pneumonia (may progress to EGPA), acute eosinophilic pneumonia, tuberculosis                                                                                                                |
| • Eosinophil-associated syndromes: EGPA, Gleich syndrome, hyper-IgE syndrome, Omenn syndrome                                                                                                                                                                                  |
| • Miscellaneous: mastocytosis, skin diseases, malignant tumors (including, but not limited to, lymphomas and leukemias), gastrointestinal disorders, hypoadrenalism, Addison disease can lead to hypoadrenalism, collagen vascular disease, drug reactions, sarcoidosis, ALPS |

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; ALPS, autoimmune lymphoproliferative syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; HIV, human immunodeficiency virus; L-HES, lymphocytic hypereosinophilic syndrome; M-HES, myeloproliferative hypereosinophilic syndrome.

<sup>a</sup>Adapted from Valent et al.<sup>10</sup>

HES.<sup>10</sup> Tissue hypereosinophilia is diagnosed when eosinophils constitute more than 20% of bone marrow nucleated cells, when there is extensive eosinophil infiltration of a tissue as determined by a pathologist, or when immunofluorescence staining demonstrates extensive extracellular eosinophil granule protein deposition in tissues, indicating local eosinophil activation.<sup>10</sup> Tissue hypereosinophilia may occur independently of peripheral blood hypereosinophilia. Criteria for diagnosis of HES or single-organ disease includes a lack of an identifiable parasitic, allergic, drug related, or other cause for the eosinophilia, requiring a detailed patient history. Clinical signs and symptoms of organ involvement attributable to eosinophilia vary along a wide spectrum based on the system affected.

Clinicians may assess for end-organ damage with initial screening studies, including blood chemical analyses for liver enzymes, creatine kinase, renal function, and troponin. Further screening for cardiac involvement may be performed, including electrocardiography and echocardiography. Lung function and integrity may be evaluated by pulmonary function testing, chest radiography, and computed tomography. Abdominal computed tomography can identify splenomegaly, lymphadenopathy, or occult neoplasms suggestive of myeloproliferative disease. Tissue biopsies may be required when these tests incite a higher level of suspicion for involvement.

Neurologic symptoms are prevalent in patients with HES and may include peripheral neuropathy and ischemic stroke.<sup>11</sup> Of these, stroke has an incidence in HES of approximately 3% to 12% and is associated with the most morbidity.<sup>11–13</sup> Stroke distribution can be in a boarder-zone pattern or in different vascular territories. In late HES, stroke in different vascular territories suggest cardiac embolism as a likely cause because of eosinophilic toxic damage to the endo-

cardium and myocardium.<sup>13</sup> However, early in the disease, transthoracic echocardiographic findings are typically normal,<sup>14</sup> which suggests that early strokes may also be caused by local thrombogenicity by tissue factor secreted by the eosinophil and induced in the endothelium.<sup>15</sup>

Echocardiography was performed to evaluate for potential causes of his cerebrovascular accident (CVA) and for cardiac damage. It was without evidence of valvular disease, a mildly depressed ejection fraction of 45% to 50%, and a negative bubble study result. Cardiac MRI showed inflammation, extensive patchy subendocardial delayed enhancement within the left ventricle, and associated edema and reduced left ventricular ejection fraction to 43%, suggestive of eosinophilic infiltration. Initial hepatic and renal function panel did not show evidence of the liver or kidney impairment. Chest computed tomography was ordered, showing scattered noncalcified nodules, calcified granuloma, and bilateral hilar adenopathy thought to be reactive in nature. There was no bronchiectasis noted, although his symptoms along with previously obstructed pulmonary function test suggest lung involvement of eosinophilia. In addition, with no other cause identified for his CVA, we considered hypercoagulability attributable to eosinophilia accounting for central nervous system involvement. We also considered sinus involvement with his history of nasal polyposis and sinus surgery.

All patients who met criteria for hypereosinophilia should have subsequent laboratory testing performed to help narrow the spectrum of diagnosis. Elevated serum tryptase and vitamin B<sub>12</sub> levels will help focus diagnosis on myeloproliferative hypereosinophilic syndromes (M-HES), whereas elevated serum immunoglobulin (specifically IgE) is often found in lymphocytic variants of hypereosinophilia (L-HES). Patients with a suggestive history of identifiable causes of eosinophilia should have further testing performed in congruence with the pertinent positive history, for example, parasitic serologic findings, human immunodeficiency virus (HIV), or antineutrophil cytoplasmic antibodies (ANCA).<sup>16</sup>

Because HES is a diagnosis of exclusion, all possible causes of our patient's condition required exploration. As noted previously, our patient had a mildly elevated IgE level before initiation of omalizumab therapy, which subsequently increased as expected, considering omalizumab prolongs the half-life of circulating IgE. He also had an elevated erythrocyte sedimentation rate (ESR) (47 mm/h) and elevated C-reactive protein level (CRP) (10.5 mg/dL), as well as an elevated vitamin B<sub>12</sub> level (1,315 pg/mL; range, 213–816 pg/mL); however, the serum tryptase level was normal (5 ng/mL). The results of infectious workup were negative for HIV, hepatitis, *Strongyloides*, and toxoplasma, and cerebrospinal fluid test results were negative for syphilis, *Cryptococcus*, herpes simplex virus, Lyme disease, cytomegalovirus, Epstein-Barr virus, mycobacterium tuberculosis, varicella zoster virus, JC virus, West Nile virus, Guillain-Barré syndrome, *Haemophilus influenzae* type b, *Neisseria*, and *Streptococcus pneumoniae*.

As part of his CVA workup, he underwent interventional radiography arteriography, the results of which were unremarkable for significant stenosis and for signs of vasculitis. An ANCA panel was also executed, looking for vasculitic causes of his symptoms, the results of which were negative. A cardiac tissue biopsy was considered to assist in ruling out EGPA, but the decision was made to postpone this invasive procedure in favor of monitoring response to pharmacotherapy. With eosinophilia documented before initiation of omalizumab treatment and no other history of medication use known to cause eosinophilia, drug reaction is unlikely in this case. To further rule out ABPA, an *Aspergillus* pricipitins panel was ordered and revealed positive IgG to *Aspergillus amstelodami* and *Aspergillus flavus* only. Serum specific IgE for these 2 strains, with negative results. Serum protein

### electrophoresis was also performed to further evaluate the IgE hypergammaglobulinemia, with normal results.

Although our patient had an elevated ESR, CRP level, and B<sub>12</sub> level, his tryptase level was normal, leaving us with some suspicion for M-HES or L-HES, whereas serologic testing results were not entirely consistent with either. In addition, he was taking a vitamin B<sub>12</sub> supplement, which may have accounted for the elevated serum level, although it is unclear to what extent. Bone marrow biopsy, including cytogenetics, should be performed for all patients with an AEC greater than 5,000 cells/mm<sup>3</sup> with features of M-HES or L-HES and could be considered in all patients with hypereosinophilia.<sup>16</sup> Finally, once a differential diagnosis is narrowed down, all patients with suspected HES should have peripheral blood examined by fluorescence in situ hybridization or reverse-transcription polymerase chain reaction for FIP1L1-PDGFR $\alpha$  fusion, clonal T-cell receptor rearrangement studies, and lymphocyte phenotyping to help in subtyping a diagnosis. On the basis of the bone marrow findings, patients with M-HES features should have additional testing for *BCR-ABL1*, *JAK2 V617F*, *KIT D816V*, *PDGFRB*, and *FGFR1* fusion genes by fluorescence in situ hybridization. For cases more consistent with L-HES and laboratory evidence of abnormal T-cell surface markers, the most common abnormality seen is CD3<sup>+</sup>CD4<sup>+</sup>. Others reported are CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup>, CD4<sup>+</sup>CD7<sup>+</sup>. T-cell clonality is demonstrated by T-cell receptor gene rearrangement studies, although this alone is not sufficient to define L-HES. Elevated IgE level or evidence of chronic active Epstein-Barr virus infection can support this diagnosis as well.<sup>17</sup> For these patients, positron emission tomography and/or lymph node biopsy should be considered.<sup>16</sup> Routine testing of family members should only be conducted if the patient's family history is strongly suggestive of eosinophilia or endomyocardial fibrosis.

**Our patient had further evaluation of possible myeloproliferative HES, with negative results for FIP1L1-PDGFR $\alpha$  fusion protein, *PDGFRB* mutation, *FGFR* mutation, and evaluation for myeloproliferative and lymphoproliferative variants of HES by bone marrow biopsy and flow cytometry. He was treated with intravenous solumedrol initially, transitioning to oral prednisone with favorable results, both normalizing eosinophil levels and controlling respiratory symptoms. As he tapered off prednisone therapy, he started treatment with mepolizumab, 100 mg subcutaneously monthly, and maintained a normal eosinophil level. With no other identifiable cause of his CVA, the cause was likely his hypercoagulable state from hypereosinophilia. His neurologic symptoms resolved through rehabilitation, and he has made a full recovery.**

EGPA remained high on the differential diagnosis throughout his workup. Both his ESR and CRP level normalized and have remained normal while receiving mepolizumab. In addition, ANCA test results were negative, and acknowledging that only 40% of patients with EGPA have a positive ANCA result,<sup>18</sup> an arteriogram was not consistent with vasculitis. Tissue biopsy samples would have been helpful in ruling out EGPA, but these were not obtained because there was no readily available source for biopsy, aside from bone marrow biopsy. A cardiac biopsy was discussed, but this invasive procedure was declined in favor of watchful waiting for continued improvement with mepolizumab. All things taken together, EGPA was thought to be less likely than HES. His eosinophil count has suppressed to zero, and he displays no signs of systemic vasculitis.

Treatment for HES should be initiated only if there is evidence of end-organ damage, which was true for our patient. Short-term treatment typically begins with a corticosteroid agent, such as 60 mg/d of prednisone in adults.<sup>16</sup> Although initial treatment is

similar for EGPA, adjunct therapies vary by disease process. Second-line therapy in patients with PDGFR $\alpha$ -negative HES who are unresponsive to corticosteroids is hydroxyurea, interferon alfa, and mepolizumab.<sup>16,19</sup> Patients with M-HES may benefit from treatment with imatinib, a BCR-ABL tyrosine kinase inhibitor.<sup>16,19</sup> Routine complete blood cell count; liver, renal, and thyroid function; and serum electrolytes must be monitored throughout this therapy. Bone marrow transplant may be required in refractory cases.<sup>16</sup> In contrast, severe cases of EGPA may be treated with a combination of glucocorticoids and cyclophosphamide or azathioprine or methotrexate. Azathioprine may be used as maintenance immunosuppressive therapy. High-dose intravenous immunoglobulin, rituximab, omalizumab, and mepolizumab have also been effective in cases.

Mepolizumab is a humanized monoclonal IgG antibody that inhibits binding of IL-5 to the  $\alpha$ -chain of the IL-5 receptor on eosinophils.<sup>20</sup> It has been used in patients with HES for compassionate use because it is currently only approved by the US Food and Drug Administration for asthma treatment.<sup>20</sup> For this patient, the dose recommended for asthma treatment, 100 mg subcutaneously monthly, has proven to be an effective steroid-sparing agent for treatment of his HES. This is a lower dose than that used by Roufosse et al.<sup>20</sup> for HES, which was 750 mg intravenously.<sup>20</sup> The subcutaneous dose used, although beneficial for our patient, may not be sufficient for others with HES.

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