

A 79-year-old man with persistent eosinophilia and elevated immunoglobulin E

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ABSTRACT

The differential diagnoses for eosinophilia include allergic, infectious, autoimmune, and neoplastic diseases. We presented the case of a 79-year-old man with eosinophilia and elevated immunoglobulin E that persisted despite adequate treatment for possible environmental exposures. Further specialized testing based on his initial workup led to his diagnosis. This case highlights the importance of sequential and targeted testing to evaluate for rare causes of eosinophilia.

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CASE PRESENTATION

Chief concern: elevated immunoglobulin E (IgE) and eosinophilia.

HISTORY OF PRESENT ILLNESS

A 79-year-old white man with history of Lyme disease, Rocky Mountain spotted fever, and recurrent pneumonia was referred to the allergy and immunology clinic for elevated IgE and eosinophilia. Approximately 3 years before presentation, he developed chest congestion and was treated with antibiotics for pneumonia. He had persistent congestion since that episode and reported productive cough with yellow-green sputum and occasional wheezing. He had no nasal congestion or dyspnea. His travel history was notable for recent trips to Africa (Botswana, Gambia, and Zimbabwe) and southeast Asia. He had never smoked. He lived in a house with mold and mice exposures but had no history of environmental allergies. His only known allergy was to penicillin. His pulmonologist found that he had elevated IgE level (1482 kU/L [reference range, 0–115 kU/L]) and eosinophilia (eosinophils, 690 cells/ μ L [reference range, 0–345 cells/ μ L]). He was referred to the allergy and immunology clinic for further evaluation.

PHYSICAL EXAMINATION

The patient's vital signs were normal. He was a well-appearing, overweight man in no respiratory distress. He had no oral lesions or lymphadenopathy. Results of a lung examination were notable for mild wheezing and rales bilaterally. He had several scaly, dry lesions on his arms and lower legs, bilaterally. Results of the rest of his physical examination were unremarkable.

QUESTION 1

What initial laboratory studies should be obtained?

Initial Laboratory and Diagnostic Findings

The white blood cell count was 6900 cells/ mm^3 (reference range, 4000–10,000 cells/ mm^3), with a differential of neutrophils, 3600 cells/ μ L (1000–9000 cells/ μ L); lymphocytes, 2100 cells/ μ L (600–4600 cells/ μ L); monocytes, 483 cells/ μ L (138–1035 cells/ μ L); eosinophils, 690 cells/ μ L (0–345 cells/ μ L); and basophils, 69 cells/ μ L (0–138 cells/ μ L). The patient's hemoglobin level was 15.3 g/dL (14–18 g/dL), platelet count was 157,000/ mm^3 (150,000–350,000/ mm^3), and sedimentation rate was 19 mm/hr (0–20 mm/hr). His IgE level was elevated to 1492 kU/L (0–115 kU/L); the other immunoglobulins were within normal limits. A computed tomography of the chest demonstrated nonspecific ground-glass nodules in the left apex and hyperinflated lungs with multifocal bronchiectasis.

QUESTION 2

What is the differential diagnosis?

- Environmental allergies
- Allergic bronchopulmonary aspergillosis (ABPA)

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- Drug induced
- Parasites
- Eosinophilic granulomatosis with polyangiitis
- Lymphocyte variant eosinophilia

When considering the differential diagnosis for our patient, it could include allergic and atopic diseases, *e.g.*, environmental allergies, ABPA, and drug-induced reactions. Although he did not have classic symptoms of environmental allergies, *e.g.*, allergic rhinoconjunctivitis, he did report exposure to mold and mice. ABPA is a possibility because he had mold exposure and respiratory symptoms. It could have been drug induced because medications associated with eosinophilia include antibiotics, nonsteroidal anti-inflammatory drugs, anticonvulsants, and herbal supplements. Drug-induced pulmonary eosinophilia is most commonly associated with nonsteroidal anti-inflammatory drugs and antimicrobials (*e.g.*, nitrofurantoin, minocycline, sulfonamides, ampicillin, and daptomycin).¹

Infectious diseases could also be considered because helminth parasites are the most common cause of eosinophilia worldwide. The patient's recent travel to Africa and southeast Asia put him at increased risk of infections with parasites, *e.g.*, *Strongyloides stercoralis*. An autoimmune cause is also on the list because eosinophilic granulomatosis with polyangiitis is a possibility. Although the patient had no rhinosinusitis symptoms, he did have pulmonary symptoms and was never diagnosed with asthma. Hematologic disorders (Hodgkin disease, T-cell lymphoma, and leukemia) and solid tumors (lung, stomach, colon, and bladder cancers) have been associated with eosinophilia. The patient had no systemic symptoms, *e.g.*, weight loss or night sweats, to suggest malignancy; however, his age was a risk factor.

QUESTION 3

What additional diagnostic studies would be helpful in clarifying the diagnosis?

Diagnostic Testing

Allergen specific IgE testing for indoor and outdoor allergens should be obtained to evaluate for possible environmental triggers. IgE and serum antibodies to *Aspergillus fumigatus* can evaluate for ABPA. Given his recent travel history, he should undergo a workup for infectious diseases, *e.g.*, stool cultures for ova and parasites, and a strongyloides serum antibody test.

If the initial testing result for environmental and infectious etiologies is negative, then he should have further testing to evaluate for less common causes of eosinophilia. Antinuclear antibody (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) are used to screen for autoimmune diseases. Flow cytometry and serum plasma electrophoresis should be obtained to

Table 1 Flow cytometry immunodeficiency panel

Flow Cytometry	Result	Reference Range
CD3 ⁺ , %	78.2	57–87
CD3 ⁺ absolute count, cells/ μ L	1642	593–2245
CD3 ⁺ CD4 ⁺ , %	61.1	30–65
CD3 ⁺ CD4 ⁺ absolute count, cells/ μ L	1283	417–1612
CD3 ⁺ CD8 ⁺ , %	47.8*	10–41
CD3 ⁺ CD8 ⁺ absolute count, cells/ μ L	1004*	149–941
CD3 ⁺ CD4 ⁺ CD8 ⁺ absolute count, cells/ μ L	754	
CD3 ⁺ CD4 ⁺ CD8 ⁺ , %	35.9	
CD4/CD8 ratio	1.28	0.7–4.9
CD3 ⁺ CD5 ⁺ , %	78.1	
CD3 ⁺ TCRgd ⁺ , %	2.2	
CD3 ⁺ CD4 ⁺ CD8 ⁺ , %	1.1	

*High

evaluate for hematologic disorders; if abnormalities are detected, then further testing, *e.g.*, bone marrow biopsy and T-cell gene rearrangements, are warranted. A bone marrow sample can be tested for mutations associated with eosinophilia, *e.g.*, platelet-derived growth factor receptor alpha (PDGFRA), platelet-derived growth factor receptor beta (PDGFRB), and c-kit.

Clinical Course

The patient's congestion resolved with inhaled corticosteroids; however, he continued to have persistently elevated IgE and mild eosinophilia. Results of environmental allergen testing were negative. *A. fumigatus* IgE, IgG, and precipitins were negative. Results of a workup for infectious diseases, including strongyloides and filariasis antibodies, were also negative. Serum plasma electrophoresis was normal. Results of a flow cytometry showed that 10% of total cells were atypical T-cells (CD3⁺ CD4⁺ CD8^{dim+} CD25⁻ Human Leukocyte Antigen–DR (HLADR⁻) CD64⁻ CD7⁺) but was otherwise unremarkable.

Despite his negative workup for infectious diseases, he was empirically treated with ivermectin due to his extensive travel history. However, his IgE and eosinophil levels did not normalize. A repeated flow cytometry was done to investigate his T-cell counts and showed an increase in CD4⁺ CD8^{dim+} CD16/56^{dim} CD3⁺ T cells with a predominance of CD45RO⁺ CD62L T cells. T-cell receptor (TCR) gene rearrangements were ordered and revealed a monoclonal T-cell population suggestive of T-cell lymphoproliferative disease (Table 1).

The patient was referred to the hematology clinic. Results of a bone marrow biopsy revealed normocellular

bone marrow, with trilineage hematopoiesis and a mild increase in interstitial T cells that comprised 5–7% of total cellularity. Results of molecular studies were negative for PDGFRA, PDGFRB, Fibroblast growth factor receptor 1 (FGFR1), D8Z2; c-kit mutation was also negative. His hematologist did not identify any evidence of active myeloproliferative syndrome, and no treatment was initiated. The patient continues to be followed up by hematology for surveillance laboratory tests and monitoring.

DISCUSSION

Eosinophilia in hematologic malignancies can be due to a primary clonal condition or a secondary reactive process.² Aside from Hodgkin lymphoma, the majority of lymphoproliferative disorders associated with eosinophilia are derived from T cells.³ T-helper type 2 (Th2) cytokines, *e.g.*, such as interleukin 5 have been associated with eosinophilopoiesis in T-cell lymphomas and Hodgkin lymphoma.^{2,4} Eosinophilia can be prognostic in certain malignancies; initial blood eosinophilia is a sign of poor prognosis and is thought to reflect Th1/Th2 imbalance in primary cutaneous T-cell lymphomas.⁵

Indolent and clinically benign T-cell lymphoproliferative disorders have also been associated with eosinophilia. In lymphocytic variant hypereosinophilic syndrome, patients have a nonmalignant expansion of a T-cell population, which produces eosinophilopoietic factors. Most patients have a benign course, but a subset of patients may progress to T-cell lymphoma. Certain phenotypes (CD3⁺/dim⁺CD4⁺, CD3⁺CD4⁺CD8⁺, and CD4⁺CD7^{dim/+}) have been linked with malignant progression.³

TCR gene rearrangement evaluates for clonality by using polymerase chain reaction and Southern blot analysis. The polymerase chain reaction test uses primers that complement five variable (V) and two joining (J) segments of the T- γ gene. Southern blot assay uses DNA probes that hybridize to the J β 1 and J β 2 regions of the TCR β chain and T- γ region of the γ chain.⁶ Simon *et al.*⁷ used the assay to investigate how often abnormal T cells are identified in persistent eosinophilia. Of 60 patients with idiopathic eosinophilia, 16 had T cells with abnormal immunophenotype and 8 had clonality detected by TCR gene rearrangement; 4 of the 16 patients were ultimately diagnosed with T-cell lymphoma or Sezary syndrome.⁷

The differential diagnosis for eosinophilia is broad, but a thorough history combined with systematic use of serologic and genetic testing can lead us to the diagnosis.⁸ Our patient had eosinophilia that could not be explained by common etiologies, such as allergic disease and parasitic infection. Flow cytometry detected atypical T cells, but molecular genetic testing with TCR gene rearrangement was necessary to identify and characterize the underlying disorder. The patient, fortunately, had no

significant symptoms of active myeloproliferative disease, but patients with T-cell lymphoproliferative disorders should be monitored for progression to T-cell lymphoma. Of patients with active myeloproliferative disease, one case reported success in the treatment of a patient with mycophenolate mofetil.⁹ Our case supports the use of TCR gene rearrangements to evaluate patients with idiopathic eosinophilia.

FINAL DIAGNOSIS

Lymphocyte variant eosinophilia secondary to T-cell lymphoproliferative disease.

CONCLUSION

We reported a case of eosinophilia and an elevated IgE level that was ultimately diagnosed as T-cell lymphoproliferative disease when a TCR gene rearrangement assay was used. Hematologic disorders should be considered in patients with eosinophilia, especially when more common etiologies, such as allergic and infectious diseases, have been ruled out. When initial testing for eosinophilia is unrevealing, sequential testing with TCR gene rearrangement can be used to identify a clonal T-cell population.

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