Eosinophilic Lung Diseases: What They Are, How They Differ

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Eosinophilia is a condition characterized by increased peripheral levels of eosinophils or eosinophilic infiltration into tissues. Jordanna Hostler, MD, Tripler Army Medical Center, Honolulu, Hawaii, USA, described eosinophilic airway diseases.

Simple pulmonary eosinophilia, or Löffler syndrome, is a disease characterized by local inflammation to a systemic parasitic infection, most commonly *Ascaris lumbricoides*. However, some drugs, such as carbamazepine and sulfas, have been reported to cause a similar reaction. Patients often present with a low-grade fever, cough, dyspnea, and hemoptysis, as well as migratory alveolar infiltrates on radiograph. For a diagnosis of Löffler syndrome, peripheral and sputum eosinophilia may be present, and *A lumbricoides* larvae may be present in the sputum, or respiratory, or gastric secretions. Treatments include inhaled bronchodilators, systemic corticosteroids, and mebendazole.

Tropical pulmonary eosinophilia is an immune hyperresponse to microfilariae of nematodes that are trapped within the lymphatic system, most commonly by *Wuchereria bancrofti*. Patients often present with a dry cough, weight loss, lymphadenopathy, and hepatosplenomegaly. Radiograph results can be normal in ≤ 30% of patients but more typically demonstrate lower-lung interstitial lesions. Peripheral eosinophilia and elevated IgE are typically present, as well as positive antibody titers for filariae. Diethylcarbamazine is an experimental agent for tropical pulmonary eosinophilia and is available by request from the US Centers for Disease Control and Prevention dispensary.

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Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to inhaled or colonizing fungal elements, most commonly to *Aspergillus* spp. Bronchiectasis occurs as a result of mycotoxins, as well as eosinophilic and neutrophilic inflammation. Patients with asthma or cystic fibrosis often present with a cough, brown mucus expectorants, fever, and eosinophilia.

Central bronchiectasis, tram lines, and ring shadows can be observed on radiography. Treatment for ABPA includes corticosteroids and azoles, such as itraconazole. Omalizumab was also found to be effective in small retrospective case studies in patients with cystic fibrosis [Lehmann S et al. *Ther Adv Respir Dis.* 2014] or asthma [Collins J et al. *J Asthma Allergy.* 2012] with ABPA.

Nonasthmatic eosinophilic bronchitis (NAEB) occurs when eosinophils infiltrate the airway in patients who do not have airway hyperresponsiveness; there have also been reports of NAEB occurring in patients with sinus disease. Patients frequently present with a chronic cough, normal radiograph results, and no evidence of airway hyperresponsiveness. Eosinophils are present in expectorated sputum or a bronchial wash, and a bronchial mucosal biopsy would reveal eosinophils. Treatment of NAEB includes inhaled corticosteroids and exposure control; montelukast is being investigated and may be an option in the future.

Andrew I. Philip, MD, Walter Reed Army Medical Center, Bethesda, Maryland, USA, discussed systemic eosinophilic syndromes with pulmonary involvement, particularly hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA). HES comprised heterogenous disorders characterized by chronic peripheral blood hypereosinophilia (HE); infiltration of eosinophils and release of mediators cause tissue damage. In 2012, a consensus was reached regarding the definitions of HES and HE based on the number of eosinophils and other criteria, recognizing that not all HES are idiopathic [Valent P et al. *J Allergy Clin Immunol.* 2012].

The 2012 consensus classified HE as

- *hereditary*, with familial clustering but an unknown pathogenesis;
- *undetermined significance*, with no clear underlying cause or family history;

- *primary* or *neoplastic*, in which eosinophils are neoplastic cells; and
- *secondary*, in which eosinophils are nonclonal and primarily cytokine driven as a result of an underlying disease or condition.

If multiorgan damage is present in addition to HE, then the disease is classified as HES. Organ damage is caused by fibrosis and thrombosis, which occur as a result of eosinophilic infiltration and the release of mediators. The treatment of HES includes glucocorticoids as first-line therapy and hydroxyurea or interferon α as second-line agents. If anti–interleukin 5 antibodies are present, mepolizumab can be used.

EGPA—previously called Churg-Strauss syndrome or allergic granulomatosis and angiitis—is a multisystem disorder that includes asthma, allergic rhinitis, and eosinophilia. Although any organ may be affected, the lungs and skin are the most common. In addition, systemic vasculitis is frequently present; however, if vasculitis is not present, it can make differential diagnosis from other eosinophilias difficult.

The exact pathogenesis of EGPA remains unknown, but it is currently thought that abnormal immune function is involved. For example, patients with EGPA exhibit increased Th1 and Th2 immunity and abnormal eosinophil function, and EGPA onset has been associated with antiasthma agents. About 40% to 60% of patients with EGPA are antineutrophil cytoplasmic antibody positive, and these patients demonstrate a higher rate of peripheral neuropathy and renal involvement but a lower rate of cardiac involvement. The course of EGPA occurs in 3 phases, which may overlap:

- the *prodromal phase*;
- the *eosinophilic phase*, in which eosinophils begin to infiltrate organs; and, finally,
- the *vasculitic phase*, in which patients experience fever, malaise, and weight loss as well as medium- and small-vessel vasculitis.

The mainstay of EGPA treatment is glucocorticoids, given at a high dose that is tapered over time, with cyclophosphamide added for patients with certain comorbidities; low-dose glucocorticoids are continued long-term for most patients. Azathioprine or methotrexate can be used during tapering of glucocorticoids or as part of a steroid-sparing regimen. Historically, patients with EGPA who did not receive treatment had about a 50% mortality rate within 3 months of the onset of the vasculitis phase. Currently, with steroid treatment, the 5-year survival rate is 70% to 90%.

Jay H. Ryu, MD, Mayo Clinic, Rochester, Minnesota, USA, discussed primary pulmonary eosinophilic syndromes. One such syndrome is acute eosinophilic pneumonia (AEP), which is a respiratory illness of known or unknown cause that includes infiltration of the lung by eosinophils. Smoking, some drugs, infections, and systemic illnesses such as HIV have been associated with AEP. Patients typically present with an acute illness ≤7 days in duration with respiratory symptoms and, potentially, fever and peripheral eosinophilia. On chest imaging, bilateral infiltrates are seen, and bronchoalveolar lavage demonstrates ≥25% eosinophils. Treatment of AEP includes high-dose corticosteroids for severe disease and prednisone for moderate disease, as well as identification and management of the underlying cause. Most patients achieve full recovery.

Chronic eosinophilic pneumonia (CEP) occurs when eosinophils infiltrate the lung as part of a chronic respiratory illness. Similar to AEP, CEP can be caused by certain drugs, such as tricyclic antidepressants and naproxen, and by infections, but it may also be caused by connective tissue diseases, such as rheumatoid arthritis, and radiation therapy used for the treatment of cancer. Patients, predominantly women, present with cough, wheezing, dyspnea, fever, night sweats, malaise, and weight loss. Up to 80% of patients will have peripheral eosinophilia, and chest imaging demonstrates bilateral patchy infiltrates. Treatment of CEP with a prolonged course of corticosteroids is typically successful; there are some reports of treatment with inhaled steroids or omalizumab. Any underlying causes should be managed, and the prognosis is typically excellent, although relapses can occur during steroid tapering.