



Hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis and other eosinophilic lung diseases

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Hypersensitivity pneumonitis (HP) is traditionally classified into acute, subacute and chronic forms. A high index of suspicion and a detailed investigation into the patient's environment is the key to diagnosis and treatment of HP. Eosinophilic lung diseases can be broadly categorized as idiopathic (acute eosinophilic pneumonia, chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndromes), those with known cause (allergic bronchopulmonary aspergillosis, drugs, parasitic and non-parasitic infections), and those associated with other known lung diseases (asthma, interstitial lung diseases and lung cancers). A detailed review of drug intake, toxin exposures, and travel history is essential in the differential diagnosis of eosinophilic lung diseases.

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Introduction

Given the constant exposure of the lungs to environmental antigens and irritants, maladaptive immune responses and eosinophilic inflammation may occur in the airways and lung parenchyma, associated with a host of respiratory diseases, including hypersensitivity pneumonitis and eosinophilic lung diseases. In the following text, we provide a focused review of these topics.

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is an inflammatory pulmonary disease that develops in response to inhalation of causative antigens, the most common of which derive from

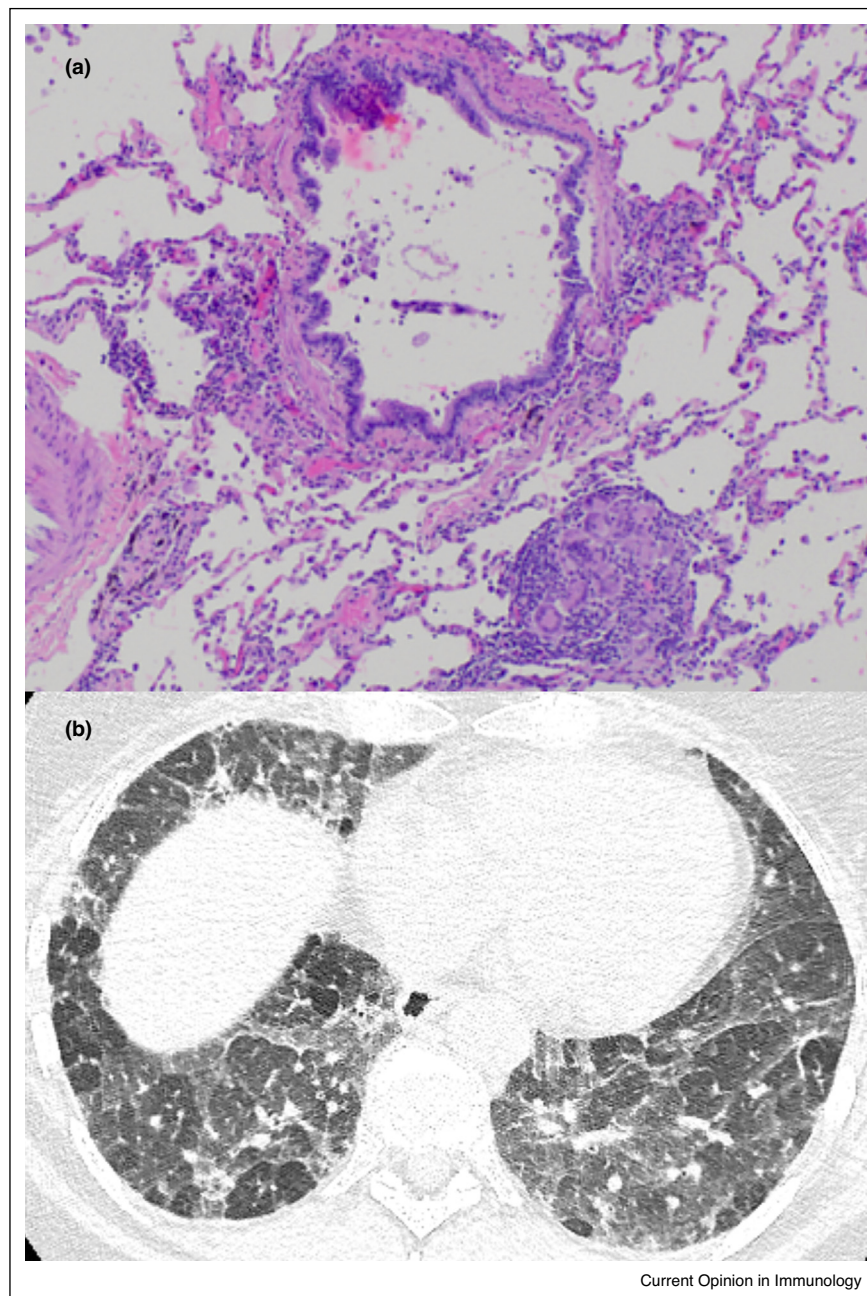
yeast, molds, fowl, and bacteria, though the cause is often unable to be identified [1,2,3^{*}]. It has historically been divided into acute, subacute, and chronic forms; however, the difficulty in distinguishing these forms and lack of prognostic value has led to proposed alternative classifications, such as classification by radiologic phenotype or into acute/inflammatory HP and chronic/fibrotic HP [3^{*},4]. Symptoms of acute HP can develop a few hours after exposure and be confused for a flu-like illness with fever, cough, dyspnea and malaise. It typically resolves if no further exposure occurs but can recur with repeat exposure [5]. Subacute and chronic HP likely result from more prolonged, low-level exposures and are characterized by more subtle onset of progressive dyspnea, fatigue and cough [5,6].

The acute form of HP is mediated predominantly through immune complexes (type III hypersensitivity) and the subacute and chronic forms through a delayed hypersensitivity (type IV) reaction [5,6]. In non-fibrotic forms of HP, biopsy reveals peribronchiolar inflammatory infiltrates with lymphocytes, plasma cells, and occasional eosinophils with associated small, non-necrotizing, poorly formed granulomas (Figure 1a) [4,6,7]. In chronic/fibrotic forms, the fibrosis can have patterns resembling usual interstitial pneumonitis (UIP) or fibrotic nonspecific interstitial pneumonia (NSIP) [7].

Given HP's heterogeneity, a high index of suspicion is necessary to make the diagnosis. A careful history is needed to find possible causative antigens and may require investigation into the patient's environment [4]. Positive antibody testing for specific antigens reflects antigen exposure and supports the diagnosis in the right clinical setting [6]. Bronchoalveolar lavage (BAL) typically reveals lymphocytosis but may be normal in some patients with chronic disease [4,5]. High-resolution computed tomography (HRCT) classically shows centrilobular micronodularity, ground-glass opacities and evidence of air trapping (mosaic attenuation), with predominantly upper and middle lobe involvement (Figure 1b) [4,5]. In chronic/fibrotic forms, HRCT can show fibrosis with reticulation, traction bronchiectasis, architectural distortion, emphysema, or honeycombing [4,5,7]. Pulmonary function testing frequently shows a restrictive pattern with reductions in the carbon monoxide diffusing capacity [6].

The cornerstone of treatment is antigen avoidance, though this can be difficult if the antigen is unknown or if avoidance causes social or economic hardship.

Figure 1



Pathological and radiological characteristics of hypersensitivity pneumonitis. Panel A — Peribronchiolar poorly formed granuloma (H&E,100×), image courtesy of Dr. Grace Lin. Panel B — Patient with chronic hypersensitivity pneumonitis. Expiratory phase imaging shows moderate air trapping with ground glass and subtle nodularity. Minimal reticulation is seen. Image courtesy of Dr. Elizabeth Weihe.

Immunosuppression with corticosteroids is widely used in chronic HP though no randomized controlled trials have demonstrated efficacy. Azathioprine and mycophenolate have been used as steroid-sparing agents though with limited evidence [8]. Acute HP tends to have a good prognosis with removal of the antigen [6]. Chronic/fibrotic forms without honeycombing are considered to have a

better prognosis than idiopathic pulmonary fibrosis (IPF), though prognosis is similar to IPF in cases with honeycombing [3*].

Eosinophilic lung diseases

Eosinophilic lung disease is an umbrella term which encompasses a range of lung diseases characterized by

Table 1**Classification of eosinophilic lung diseases****Known cause:**

1. Allergic bronchopulmonary aspergillosis (ABPA)
2. Drugs, toxins & radiation: antibiotics, NSAIDs, inhaled drugs of abuse (e.g. cocaine), scorpion sting, particulate metals, radiation therapy etc.
3. Non-parasitic infections: fungal (coccidiomycosis, paracoccidiomycosis), TB
4. Parasitic infection:

	Syndrome	Parasites
a.	Löffler's syndrome	<i>Ascaris</i> , hookworm, <i>Strongyloides</i>
b.	Hyperinfection syndrome	<i>Strongyloides</i>
c.	Tropical pulmonary eosinophilia	<i>Wuchereria bancrofti</i>
d.	Cystic lung disease	<i>Echinococcus</i> (dog tape worm), <i>Cysticercosis</i> (pork tape worm)
e.	Visceral larva migrans	<i>Toxocara</i> (dog & cat round worm)
f.	Direct lung invasion	<i>Paragonimus</i> (lung fluke)

Idiopathic (primary eosinophilic lung diseases):

Lung limited	Multi-organ system involvement
1. Acute eosinophilic pneumonia (AEP)	1. Hypereosinophilic syndromes (HES)
2. Chronic eosinophilic pneumonia (CEP)	2. Eosinophilic granulomatous with polyangiitis (EGPA)

Associated with other pulmonary diseases:

1. Asthma & eosinophilic bronchitis
2. ILD: cryptogenic organizing pneumonia, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, sarcoidosis, eosinophilic granuloma, connective tissue disease
3. Malignancy: non-small cell lung cancer, non-Hodgkin's lymphoma, myeloblastic leukemia, metastatic disease

eosinophilic infiltration of the pulmonary parenchyma and often associated with peripheral eosinophilia. Table 1 describes a classification system for eosinophilic lung diseases [9].

Allergic bronchopulmonary aspergillosis (ABPA)

Aspergillus is a ubiquitous mold which can colonize the airways. In patients with asthma and cystic fibrosis, colonization with this mold can cause antigenic sensitization leading to a complex hypersensitivity reaction. Sensitized CD4⁺ T-cells generate a Th2-inflammatory response, releasing Interleukin (IL)-4, IL-5, and IL-13. This, in turn, drives eosinophil recruitment to the airways, blood eosinophilia, elevated IgE levels, and ultimately, airway damage [10].

ABPA manifests in 1–2% of patients with persistent asthma and 2–15% of patients with cystic fibrosis [11]. Patients classically present with recurrent exacerbations of their underlying asthma or bronchiectasis, wheezing, cough productive of brown mucus plugs, and occasionally hemoptysis and fever. Laboratory studies reveal peripheral eosinophilia, elevated serum IgE levels, *Aspergillus*-specific serum IgE or immediate skin test reactivity to *Aspergillus*, and *Aspergillus*-specific serum IgG and/or *Aspergillus*-specific serum precipitins. Chest imaging typically shows central and upper lobe predominant bronchiectasis, migratory infiltrates, high attenuation mucus (HAM) and gloved finger shadows [12,13]. We prefer to

Table 2
Diagnostic criteria for allergic broncho-pulmonary aspergillosis, as proposed by International Society for Human and Animal Mycology (ISHAM) working group in 2013 [14]
Predisposing condition (one must be present):

1. Asthma
2. Cystic fibrosis

Obligatory criteria (both must be present):

1. *Aspergillus* skin test positivity or elevated IgE levels against *Aspergillus fumigatus*
2. Elevated total IgE concentration (typically >1000 IU/mL, but if the patient meets all other criteria, an IgE value <1000 IU/mL may be acceptable)

Other criteria (at least two must be present):

1. Precipitating serum antibodies to *A. fumigatus* or elevated serum *Aspergillus* IgG by immunoassay
2. Radiographic pulmonary opacities consistent with ABPA
3. Total eosinophil count >500 cells/μL in glucocorticoid-naïve patients (may be historical)

use the simplified diagnostic criteria for ABPA elucidated in Table 2 [14,15].

Acute or recurrent ABPA is treated with a combination of corticosteroids and anti-fungal therapy [16]. Monthly total serum IgE is used to monitor therapy such that a 35% decrease is considered a good clinical response and tapering is considered appropriate. Oral Itraconazole for 16 weeks is the antifungal therapy of choice [17]. Newer agents such as voriconazole and posaconazole are acceptable alternatives, respectively, with isavuconazole being

used in case reports [18]. Azole therapy may be limited by hepatotoxicity and gastrointestinal symptoms. Once in remission, where patients have typically been weaned off corticosteroid therapy with no radiologic infiltrates and a suppressed IgE level, anti-fungal therapy is not recommended, and inhaled corticosteroids are used to treat and control underlying asthma. Patient with refractory disease are steroid-dependent, and biologic therapies including omalizumab and mepolizumab have shown promising results [19].

Drug, toxin & radiation associated

A variety of drugs can cause pulmonary infiltrates and peripheral eosinophilia. Classically described drugs include non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics (e.g. nitrofurantoin, daptomycin, minocycline) [20]. Because of the extensive list of drugs which can cause such a reaction, a detailed review of the medication list to exclude possible offending agents is warranted. Exposure to inhaled recreational drugs (including crack cocaine), particulate metals and scorpion stings have been associated with pulmonary eosinophilia. Clinical features may vary on a spectrum, from asymptomatic to an acute pneumonia presentation. Treatment is avoidance of the offending agent, and a limited course of corticosteroids may be needed to control severe symptoms. Radiation therapy and food allergies have also been reported to cause eosinophilic pneumonia [21]. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a distinct clinical entity associated with certain anti-epileptics and other medications, including antibiotics, which may present with fever, rash, lymphadenopathy, peripheral eosinophilia and organ involvement including pulmonary infiltrates.

Infection-associated

In 1932, Löffler first described the association between pulmonary infiltrates and eosinophilia with *Ascaris* as the suspected cause, earning the name 'Löffler's syndrome' [22]. Several helminthic infections can cause pulmonary eosinophilia and present as distinct clinical syndromes. Therefore, parasitic pulmonary eosinophilia can be classified either by causative organism or by the clinical syndrome (Table 1). Eliciting a travel history to tropical climates and endemic regions is of particular importance, including barefoot exposure to water bodies and ingestion of certain meats. Parasitic infections (particularly *Strongyloides*) should be excluded in patients with eosinophilic lung disease before initiation of immunosuppressive therapy. The extent of investigations necessary to exclude parasitic infections is variable and contingent upon clinical suspicion and local experience. Non-parasitic infections including endemic fungal infections (coccidiomycosis, paracoccidiomycosis and basidiobolomycosis) can be associated with pulmonary eosinophilia [23]. *Pneumocystis jirovecii* pneumonia, mucormycosis and tuberculosis

(TB) have also been reported to cause pulmonary infiltrates with eosinophilia.

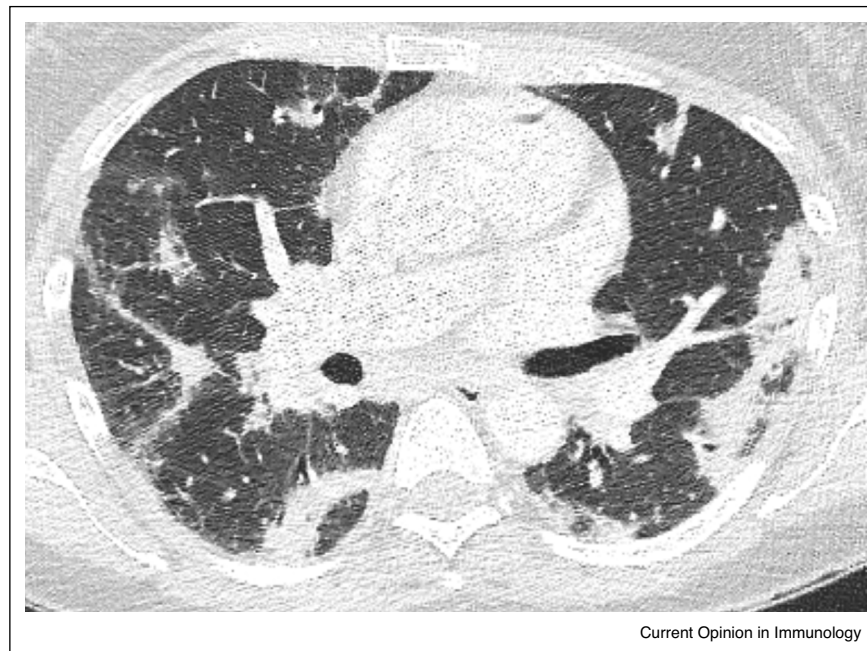
Acute eosinophilic pneumonia

Acute eosinophilic pneumonia (AEP) is an idiopathic eosinophilic lung disease characterized by an acute presentation, clinically indistinguishable from acute respiratory failure due to acute respiratory distress syndrome (ARDS). Peripheral eosinophilia is typically absent, and diagnosis is revealed by a BAL with >25% eosinophils. The disease has been associated with new initiation of cigarette smoking, though an inciting cause is most often not identified [24]. A detailed history to rule out other causes including parasites, environmental exposures and drugs is key [24]. Signs and symptoms include cough, dyspnea, fever, crackles, rhonchi and hypoxemia. The clinical course is often rapidly progressive to acute respiratory failure, requiring endotracheal intubation. Chest X-ray shows diffuse bilateral pulmonary infiltrates and HRCT may reveal ground glass opacities, reticular infiltrates, and small pleural effusions. If pleural effusions are present, cell counts of the pleural fluid show eosinophilia. Lung biopsy is not a usual component of AEP diagnosis, but if done, biopsy usually reveals eosinophilic infiltrates with areas of organization and diffuse alveolar damage. AEP is characterized by a dramatic response to corticosteroids with often complete resolution of pulmonary infiltrates over several weeks and an overall excellent prognosis [25]. Steroid responsiveness and absence of other organ involvement are clues to diagnosis of AEP.

Chronic eosinophilic pneumonia

Chronic eosinophilic pneumonia (CEP) has several contrasting features with AEP [26]. CEP has a subacute to chronic clinical course with cough, wheezing, night sweats and dyspnea progressive over several weeks to months. CEP has a female to male predominance and is often associated with pre-existing asthma. Peripheral eosinophilia is a characteristic of CEP, which is typically absent at AEP onset. BAL shows elevated eosinophil counts with a differential typically over 40%. Chest imaging shows airspace infiltrates which have classically been described as peripheral, though need not necessarily occur in that distribution (Figure 2). Lung biopsy is usually not necessary, but reveals eosinophilic parenchymal infiltrates, organizing pneumonia and minimal fibrosis. Similar to AEP, CEP responds very well to corticosteroid therapy, but often requires a prolonged course over months to years with a slow taper, given the high relapse rate off therapy [27]. The differential diagnosis includes EGPA and HES, though both of these entities often have significant extra-pulmonary involvement. EGPA and CEP in particular share significant overlap in that they are chronic eosinophilic lung diseases, affecting individuals with pre-existing asthma, associated with peripheral eosinophilia and elevated IgE levels.

Figure 2



Axial CT image with peripheral consolidations and opacities in a patient with chronic eosinophilic pneumonia. Image courtesy of Dr. Elizabeth Weihe.

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg Strauss syndrome) is a rare, multi-system disorder associated with asthma and hypereosinophilia, characterized by eosinophil-rich and necrotizing granulomatous inflammation and a small-to-medium vessel necrotizing vasculitis [28,29]. EGPA is typically included in the spectrum of antineutrophilic cytoplasmic antibody (ANCA)-positive vasculitides, though only 30–40% of patients are ANCA-positive, typically in a perinuclear pattern with myeloperoxidase (MPO) specificity [30].

Classically, EGPA has been described evolving through three phases — the prodromal phase, eosinophilic infiltration phase, and the vasculitic phase. However, patients often do not follow this classic pattern. EGPA often presents in the fifth to sixth decade of life with severe asthma being the most prominent feature. Asthma is present in approximately 90% of patients at diagnosis and typically precedes the diagnosis by 9–11 years [29,30]. Upper respiratory symptoms such as nasal polyps, allergic rhinitis, and sinusitis are also common [31]. Some vasculitic findings such as peripheral neuropathy, purpura, and renal disease are more common in ANCA-positive patients, while cardiac involvement is more prominent in ANCA-negative patients, though substantial overlap in the clinical characteristics of ANCA-positive and ANCA-negative

patients exist [30]. Often these patients require oral corticosteroids for asthma control and can manifest with EGPA when steroids are tapered, such as when leukotriene inhibitors or omalizumab treatments improve asthma control [32].

The diagnosis is largely clinical, though multiple definitions and diagnostic criteria have been developed such as the American College of Rheumatology and Chapel Hill criteria [32]. We favor the definition used in a recent pivotal trial of the anti-IL-5 monoclonal antibody mepolizumab in EGPA: asthma plus eosinophilia ($>1.0 \times 10^9/L$ and/or 10% of leukocytes) plus two additional features — biopsy showing histopathologic evidence of eosinophilic vasculitis, neuropathy, pulmonary infiltrates (non-fixed), sino-nasal abnormality, cardiomyopathy by echo or magnetic resonance imaging (MRI), glomerulonephritis, alveolar hemorrhage, palpable purpura, or a positive ANCA [33^{*}]. Though serum ANCA is frequently negative, sputum ANCA has potential as a possible biomarker [34^{**}].

When suspected, the extent of organ involvement should be investigated to help make the diagnosis, assess prognosis, and determine initial treatment. Cardiac involvement, in particular, is the leading cause of death and can be assessed with electrocardiogram, echocardiogram, or cardiac MRI [35]. In low-risk patients, corticosteroid

therapy alone is first line and can often achieve remission. In higher-risk patients or those who fail corticosteroids, additional immunosuppression, such as with cyclophosphamide or rituximab, should be added [31]. More recently, mepolizumab has been demonstrated to be effective in treatment of EGPA and is FDA approved for this indication [33*,36].

Hypereosinophilic syndromes

The hypereosinophilic syndromes (HES) encompass a broad group of illness defined by marked peripheral eosinophilia (generally $>1500/\text{mm}^3$) on at least two occasions or significant tissue eosinophilia associated with symptoms and blood eosinophilia, independent of alternative causes [37]. Disease manifestations can range from asymptomatic to multiple end-organ failure [38].

HES has multiple subtypes distinguished by the underlying driver of eosinophil proliferation, though many patients are categorized as idiopathic. Myeloid HES variants have characteristics of other myeloproliferative disorders. These patients may have a detectable mutation on cytogenetic analysis associated with a myeloproliferative process. A subset of patients with myeloid HES have a fusion of the Fip1-like1 (FIP1L1) and platelet-derived growth factor receptor alpha (PDGFRA) genes and respond to treatment with imatinib.

T-cell lymphocytic HES is driven by aberrant T-cell clones (most commonly $\text{CD3}^+\text{CD4}^+$) that may produce eosinophil hematopoietins such as interleukin-5 (IL-5). There are also familial forms of inherited eosinophilia as well as clonal eosinophilia, such as in chronic eosinophilic leukemia [38].

Management is typically aimed at suppression of the eosinophilia to reduce the end-organ damage. Corticosteroids have widely been used for this, as well as hydroxyurea, interferon- α , and imatinib as mentioned above. Anti-eosinophil therapy with targeted monoclonal antibodies, such as mepolizumab and reslizumab (anti-IL-5) and more recently, benralizumab (monoclonal antibody against IL-5 receptor component IL-5R α), have shown promise [38,39*].

Conclusions

A high index of suspicion is necessary to diagnose hypersensitivity pneumonitis and eosinophilic lung diseases. Careful attention to BAL cell counts and peripheral blood differential can yield important clues to the diagnosis of eosinophilic lung diseases in particular.

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Conflict of interest statement

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