Differential Diagnosis of Eosinophilic Lung Diseases

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Learning objectives:

1. Identify infectious, hematologic, allergic, and autoimmune diseases that may cause pulmonary eosinophilia.

2. Differentiate between primary eosinophilic lung syndromes and secondary causes through careful clinical, radiologic, and laboratory evaluation.

3. Apply structured diagnostic algorithms and evidence-based strategies to improve accuracy in the differential diagnosis of eosinophilic lung diseases.

4. Recognize overlapping clinical presentations and avoid common pitfalls that may delay or misdirect diagnosis.

5. Integrate best practices into patient care to ensure timely and appropriate management tailored to the underlying etiology.

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Abbreviations used
ABPA- allergic bronchopulmonary aspergillosis
AEP- acute eosinophilic pneumonia
ANCA- antineutrophil cytoplasmic antibody
BAL- bronchoalveolar lavage
CEP- chronic eosinophilic pneumonia
CTD- connective tissue disease
EGPA- eosinophilic granulomatosis with polyangiitis
ELD- eosinophilic lung disease
HE- hypereosinophilia
HES- hypereosinophilic syndrome
HRCT- high-resolution computed tomography
i-HES- iopathic HES
ILD- interstitial lung disease
L-HES- lymphocytic-variant HES
OP- organizing pneumonia
M-HES- clonal myeloid HES
MMF- mycophenolate mofetil

ABSTRACT: Eosinophilic lung diseases encompass a heterogeneous spectrum of disorders characterized by the accumulation of eosinophils within the lung parenchyma. Etiologies range from primary eosinophilic syndromes to secondary causes such as parasitic and fungal infections, hematologic malignancies, allergic conditions, and systemic autoimmune diseases. Given their overlapping clinical and radiologic presentations, accurate and timely diagnosis is critical for guiding appropriate management and avoiding both overtreatment and delays in therapy. This review synthesizes current evidence and expert perspectives on the differential diagnosis of eosinophilic lung diseases, drawing on clinical, laboratory, radiologic, and histopathologic approaches. Key emphasis is placed on distinguishing primary eosinophilic syndromes from secondary causes, the role of molecular and immunologic testing, and the integration of multidisciplinary expertise. A comprehensive diagnostic algorithm is presented to assist clinicians in routine practice, with particular emphasis on addressing unmet needs such as biomarker development and the establishment of standardized definitions for disease activity. By elucidating diagnostic processes and minimizing common errors, this article seeks to enhance the precision of differential diagnosis and improve clinical outcomes for patients with eosinophilic lung involvement. **(J Allergy Clin Immunol Pract 2026;14:542-57)**

Key words: *Eosinophilic lung disease; Eosinophilic granulomatosis with polyangiitis; Allergic bronchopulmonary aspergillosis; Chronic eosinophilic pneumonia; Hypereosinophilic syndrome; Mepolizumab*

INTRODUCTION

Eosinophilic lung diseases (ELDs) represent a heterogeneous spectrum of disorders characterized by the accumulation of eosinophils within 1 or more pulmonary compartments, including the pulmonary parenchyma and/or airspaces, often accompanied by peripheral blood or bronchoalveolar lavage (BAL) eosinophilia. Although considered rare, they pose significant diagnostic challenges due to overlap with infectious, interstitial, airway, malignant conditions (including T-cell and B-cell lymphomas), and vasculitic lung diseases, and may lead to severe outcomes if unrecognized.[1] Epidemiological data remain limited, but ELDs are likely underdiagnosed because of their nonspecific clinical and radiological presentation. Peripheral eosinophilia is not invariably present, and occasionally, diagnosis relies on BAL or tissue findings demonstrating pulmonary eosinophilic infiltration.[1]

A pragmatic classification distinguishes primary (ie, idiopathic) ELDs, such as acute eosinophilic pneumonia (AEP) and chronic eosinophilic pneumonia (CEP), from secondary forms associated with identifiable causes including parasitic or fungal infections, drug exposure, hematologic malignancies, allergic airway disorders (eg, allergic bronchopulmonary aspergillosis [ABPA]), and systemic autoimmune or vasculitic diseases such as eosinophilic granulomatosis with polyangiitis (EGPA).[1] This distinction is clinically relevant because secondary forms require both treatment of the underlying condition and suppression of eosinophilic inflammation.

ELDs manifest with nonspecific respiratory symptoms (cough, dyspnea, wheeze), constitutional signs (fever, weight loss), and radiological abnormalities including ground-glass opacities, consolidations, or nodules. Blood and BAL eosinophilia vary according to disease subtype.[1] Pathologically, ELDs feature eosinophilic infiltration of alveoli, interstitium, and small airways, driven by T_H2-skewed immune responses involving IL-5, IL-13, and GM-CSF, resulting in tissue damage and remodeling.[2]

The diagnostic challenge lies in recognizing eosinophilic patterns of lung involvement, differentiating idiopathic from secondary causes, and integrating serological, radiological, and histopathologic data within a multidisciplinary approach. Structured diagnostic algorithms for pulmonary eosinophilia have been shown to improve diagnostic efficiency and reduce misclassification.[1] With the increasing availability of targeted biologic therapies directed at IL-5 or its receptor, a clear diagnostic framework is even more essential for timely and appropriate management.

This review provides an overview of the latest evidence regarding ELDs, focusing on infectious, hematologic/oncologic, allergic/airway, and autoimmune/systemic causes. It also offers a practical diagnostic algorithm (Figure 1) and clinical-radiologic-pathologic correlations (Tables I-III) to help clinicians with the differential diagnosis and management of ELDs.

INFECTIOUS ETIOLOGIES

In the diagnostic evaluation of ELDs, infectious etiologies should be systematically considered as potentially reversible drivers of pulmonary eosinophilia, ideally before initiating glucocorticoids or other immunosuppressive therapy. Parasitic infections are the most frequently implicated worldwide, followed by fungal pathogens. Bacterial and viral associations are less well characterized but may warrant consideration in the appropriate epidemiologic and clinical contexts. The main infectious etiologies and related laboratory and clinical features are summarized here.

Parasitic infections

Most parasitic infections induce pulmonary eosinophilia through larval migration across the pulmonary vasculature and

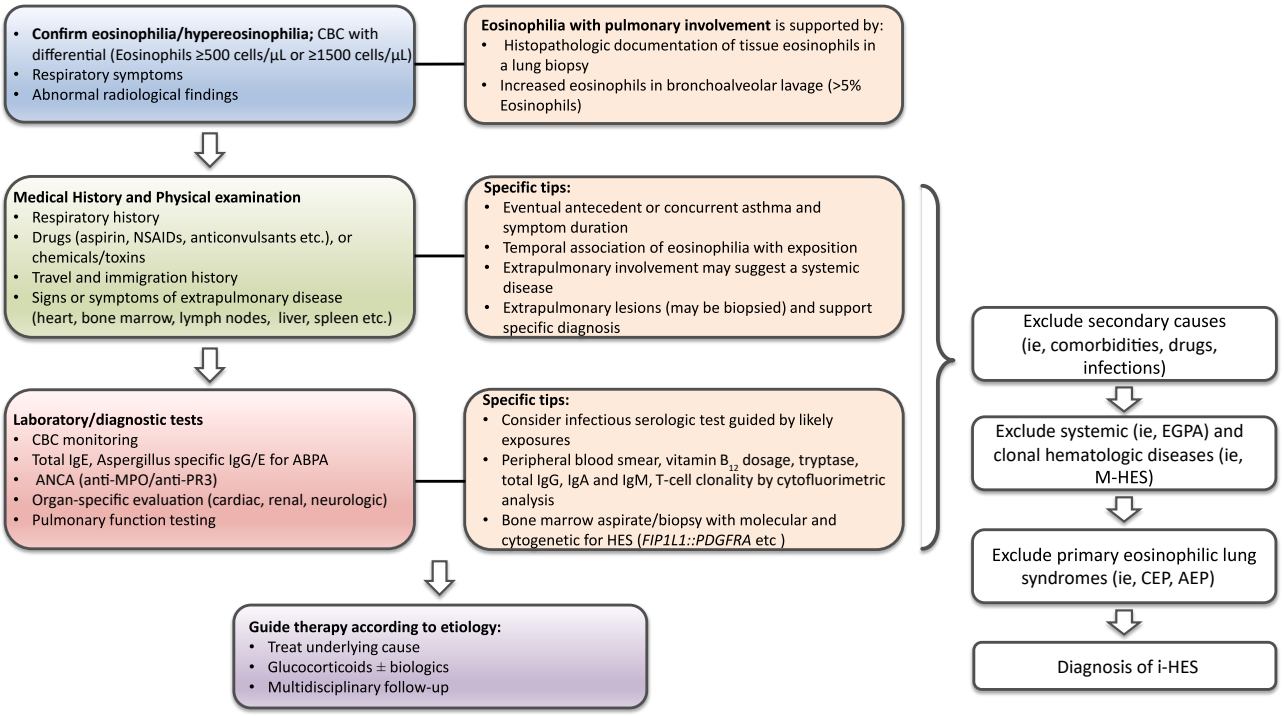

FIGURE 1. Diagnostic algorithm for pulmonary eosinophilia. *CBC*, Complete blood cell count; *IAEP*, idiopathic AEP; *ICEP*, idiopathic CEP; *NSAID*, nonsteroidal anti-inflammatory drug.

TABLE I. Differential diagnosis of pulmonary eosinophilia by clinical context

Clinical setting	Key clues	Most likely etiologies	First-line tests
Acute febrile illness in young adult	Rapid dyspnea, fever, diffuse infiltrates	AEP, parasitic infection, EGPA	BAL, stool exam, HRCT, ANCA
Chronic asthma with recurrent infiltrates	Wheezing, high IgE, bronchiectasis	ABPA, CEP, EGPA	Total IgE, Aspergillus IgE/IgG, ANCA, HRCT
Systemic features (fever, neuropathy, purpura)	Multisystem involvement	EGPA, HES, hematologic malignancy	CBC, ANCA, bone marrow, molecular testing
Immunosuppressed patient	High-risk exposures, severe infection	*Strongyloides* hyperinfection, fungal pneumonia	BAL, serology, cultures

CBC, Complete blood cell count.

parenchyma, provoking an eosinophil-rich inflammatory response and respiratory symptoms. In soil-transmitted helminth infections, this manifests as a transient eosinophilic pneumonia, commonly referred to as Loeffler's syndrome.[21] In other settings, pulmonary disease reflects a pronounced hypersensitivity reaction to a systemic parasite, as seen in tropical pulmonary eosinophilia triggered by *Brugia malayi* or *Wuchereria bancrofti*. Tropical pulmonary eosinophilia can mimic both AEP and CEP. Nocturnal exacerbations are common in tropical pulmonary eosinophilia, which is characterized by markedly elevated absolute eosinophil counts ($>3.0 \times 10^9$/L), IgE levels (>1.000 U/mL), and antifilarial antibody levels. If unrecognized, it may progress to chronic disease and ultimately, pulmonary fibrosis.[22,23]

The pretest probability of parasitic infection hinges on exposure history in patients with compatible clinical features. Questions to include in the patient interview include birthplace, destinations and durations of travel, residence in rural settings, contact with livestock, occupation, and consumption of undercooked meat/seafood or exotic meats. Among individuals who have not traveled outside the Western Hemisphere, the most common parasitic causes of pulmonary eosinophilia are soil-transmitted helminths, including *Ascaris lumbricoides*, hookworm, and *Strongyloides stercoralis*. Risk is increased in children, those living in poverty, residents of rural areas, and those who engage in agricultural work or jobs that entail frequent contact with contaminated soil or animal waste (eg, plumbers, electricians, and exterminators).[24]

Although most pulmonary presentations of parasitic infections are not life-threatening, a notable exception is *Strongyloides* hyperinfection syndrome. Because of the global prevalence of *S stercoralis* and its capacity for autoinfection, chronic asymptomatic carriage is common. Exposure to substantial immunosuppression, particularly glucocorticoids, can precipitate accelerated autoinfection with massive larval migration and tissue invasion, resulting in acute respiratory distress

TABLE II. Key distinguishing features of major ELDs

Disease	Onset	Blood eosinophilia	BAL eosinophilia	Imaging	Relapse	Systemic involvement
CEP	Subacute (wk)	High	>40%	Peripheral consolidations	Common	No
AEP	Acute (<1 mo)	Often absent at onset	>25%	Diffuse ground-glass, pleural effusion	Rare	No
ABPA	Subacute	Moderate-high	Variable	Central bronchiectasis, mucus plugs	Yes	Asthma, rhinosinusitis
EGPA	Subacute/chronic	High	>25%	Migratory opacities, nodules	Yes	Multisystem (neuropathy, skin, heart)
HESs	Subacute/chronic	Very high	Variable	Ground-glass opacities, nodules, pleural effusions	Variable	Multiorgan involvement
Parasitic infections	Acute/subacute	High	>25%	Transient or fixed infiltrates; nodules; pleural effusions	No	Extrapulmonary symptoms (fever, gastrointestinal, skin)

TABLE III. Pulmonary involvement in autoimmune and systemic eosinophilic diseases

Disease	Key pulmonary features	Typical HRCT findings	Diagnostic clues	Therapy and prognosis	References
EGPA	Adult-onset asthma, cough, dyspnea, migratory or transient infiltrates, occasionally DAH	Peripheral or subpleural consolidations, ground-glass opacities, nodules, pleural effusion	Asthma, blood eosinophilia $> 1 \times 10^9$/L, ANCA + (30%-40%), systemic vasculitic features (neuropathy, purpura, GN)	Rapid glucocorticoid responsiveness; anti−IL-5/IL-5R biologics (mepolizumab, benralizumab) reduce relapse; recurrent infiltrates predict relapse	[1,3-8]
CTD-associated eosinophilic ILD (eg, SSc, RA, and SLE)	Cough, dyspnea, restrictive PFTs, sometimes acute exacerbations with BAL eosinophilia	Ground-glass opacities, reticulation, NSIP- or OP-like patterns	Autoantibody positivity (ANA, anti-RNP, anti-Scl70), systemic CTD features	Glucocorticoids ± MMF or AZA or RTX; prognosis depends on CTD subtype	[9-12]
Drug-induced eosinophilic pneumonia	Acute/subacute dyspnea, fever, diffuse infiltrates temporally linked to new drug	Bilateral GGOs, patchy consolidations, OP-like changes	Recent exposure (eg, biologics and immunomodulators); resolution after withdrawal	Discontinuation plus short glucocorticoid course; excellent prognosis	[12,13]
HESs (idiopathic or clonal)	Cough, wheeze, dyspnea, pleural effusions; may mimic asthma	Patchy opacities, nodules, reticulation, sometimes cardiac enlargement	Blood eosinophilia $> 1.5 \times 10^9$/L; multiorgan involvement (heart, skin, GI); FIP1L1-PDGFRA testing	Glucocorticoids; imatinib if FIP1L1-PDGFRA+; anti−IL-5/IL-5R therapy for appropriate and/or refractory disease. Prognosis varies by subtype and extent of organ involvement	[14-20]
Undifferentiated systemic eosinophilic disorders/ overlap syndromes	Asthma, sinusitis, migratory infiltrates, systemic symptoms without defined vasculitis	Mixed OP + GGO patterns, recurrent	Peripheral eosinophilia, negative ANCA, exclusion of infection/ malignancy	Empirical glucocorticoids; monitor for evolution to EGPA or HES	[1,12,13]

AZA, Azathioprine; *DAH*, diffuse alveolar hemorrhage; *GGO*, ground-glass opacity; *GN*, glomerulonephritis; *NSIP*, nonspecific interstitial pneumonia; *PFT*, pulmonary function test; *RA*, rheumatoid arthritis; *RTX*, rituximab; *SLE*, systemic lupus erythematosus; *SSc*, systemic sclerosis.

TABLE IV. Parasitic etiologies of eosinophilic lung disease

Predominant radiographic feature	Pathogen	Geography	Peripheral eosinophilia	Clinical pearls
Migratory infiltrates				
	Ascariasis *Ascaris lumbricoides*	Worldwide	+/++	Stool ova and parasite examination result is typically negative at this stage; diagnosis is usually clinical (exposure + eosinophilia + transient infiltrates); stool ova and parasite become more informative later in the intestinal phase; children and those exposed to pig farming are at highest risk
	Hookworm *Ancylostoma duodenale* *Necator americanus*	Worldwide	+/++	Working as farmers, plumbers, exterminators, etc or walking barefoot on beaches (especially dog beaches) is a risk factor; confirm with stool ova and parasite examination once intestinal infection is established (pulmonary phase may precede stool positivity)
	Strongyloidiasis *Strongyloides stercoralis* (acute infection)	Worldwide	+/++	Walking barefoot and living in rural areas increase risk; autoinfection enables Strongyloidiasis to persist for decades; serology is the preferred screening test; a single stool exam is poorly sensitive in chronic infection
Diffuse infiltrates				
	Strongyloides hyperinfection syndrome *Strongyloides stercoralis*	Worldwide	−/+	Occurs days to weeks after initiation of immunosuppression in a chronically infected host; life-threatening if not identified quickly Respiratory distress, abdominal pain, rash, and gram-negative bacteremia are common features Diagnosis requires urgent evaluation with serial stool/sputum (or BAL) for larvae; do not rely on a single negative test result, start empiric ivermectin if suspicion is high and immunosuppression is present or imminent
	Tropical pulmonary eosinophilia *Wuchereria bancrofti*, *Brugia malayi*	Asia, Africa, South America (Guyana). India with highest concentration	+++	Requires repeated mosquito bites (over months to years) in an endemic area. Middle-aged adults are most at risk. Cough/wheeze that is worsens at night is a key feature; hepatosplenomegaly and lymphadenopathy can be seen; supportive testing includes antifilarial antibodies together with very high eosinophilia and IgE in an exposed patient
Pulmonary nodules				
	Visceral Larva Migrans *Toxocara canis* *Toxocara cati*	Worldwide	++++	Almost exclusively occurs in children; sandboxes and outdoor cats/canids are risk factors Causes multisystem involvement: hepatic, pulmonary, ocular, CNS Diagnosis is supported by Toxocara serology in the appropriate exposure/clinical context (stool ova and parasites is not diagnostic in humans)
	Katayama fever *Schistosoma hematobium* *Schistosoma mansoni*	Africa, Middle-East, Asia, South America	+++	Initially manifests as fever, hepatosplenomegaly, pulmonary involvement Occurs 3-8 wk after heavy skin exposure to contaminated freshwater; may become chronic Early diagnosis is usually serologic; ova detection in stool/urine may be negative in the acute (Katayama) phase

	Dirofilariasis *Dirofilaria immitis*	Worldwide	−/+	Caused by bites from mosquitos infected by dogs or wildlife with heartworm infection Typically a single solid nodule that is found incidentally and may mimic malignancy Symptomatic patients may have cough, chest pain, fever, and cutaneous or ocular nodules Definitive diagnosis is most often histopathologic after biopsy/resection of a solitary pulmonary nodule
Cystic lesions				
	Pulmonary Echinococcosis *Echinococcus granulosus*, *Echinococcus multilocularis*	Worldwide	−/+	Exposure to outdoor dogs in farming areas is a risk factor Hepatic cysts are almost always present as pulmonary spread is secondary; cysts slowly grow over months to years; cyst rupture causes eosinophil spikes and anaphylaxis Diagnosis relies on characteristic imaging plus echinococcal serology; avoid aspiration/biopsy unless necessary due to risk of cyst rupture and anaphylaxis
Pulmonary effusion				
	Sparganosis (*Spirometra* spp.)	Asia, Central and South America, Brazil with highest concentration	+/++	Caused by ingestion of contaminated water or undercooked frogs/snakes; can occur weeks to years after exposure Pulmonary presentation may mimic eosinophilic pneumonia; in addition to the lungs, larvae may disseminate to the skin (“creeping tumor”), CNS, and abdominal viscera Diagnosis is often confirmed by tissue identification when accessible; serology may support the diagnosis in compatible exposure
Mixed radiographic findings				
	Paragonimiasis (*Paragonimus* spp.)	Asia, parts of Africa and the Americas (*P kellicotti* in North America)	++	Caused by ingestion of undercooked crabs/crayfish or paratenic hosts (wild boar/pork); around 1/5 cases are incidentally found May mimic tuberculosis or fungal infection with pleuritic chest pain, hemoptysis, fevers, malaise Confirm with ova detection in sputum (or stool) and/or paragonimus serology in the appropriate exposure setting

CNS, Central nervous system.

syndrome, gram-negative bacteremia, and cutaneous eruptions, among other systemic features.[25] Mortality can be as high as 87% if recognition is delayed.[26,27] To prevent this complication, any patient under consideration for immunosuppression should be assessed for epidemiologic risk and screened with *Strongyloides* serologic tests, which carry approximately 90% sensitivity and specificity.[28] A single stool examination is an unreliable exclusion test in chronic infection due to low parasitic load and intermittent shedding.[29] When immunosuppressive agents are indicated in a patient with high clinical suspicion for strongyloidiasis based on exposure history, empiric ivermectin (200 μg/kg/d for 2 doses) is a low-risk, preventive strategy warranted to avert severe outcomes, irrespective of serologic results.[30-32]

Table IV summarizes parasitic etiologies of pulmonary eosinophilia. Pulmonary involvement in loiasis, mansonellosis, amebiasis, and lophomoniasis has been reported in the literature. However, pulmonary presentations are atypical in these infections and are not included in the table.[33-35]

There is no single set of laboratory, radiographic, or clinical features that reliably distinguishes parasitic from nonparasitic causes of pulmonary eosinophilia. If epidemiologic risk factors are present, early consultation with an infectious disease specialist experienced in tropical medicine is recommended, because diagnosis and management are nuanced and often rely on serologic testing, which can be affected by cross-reactivity and interpretive variability.

Fungal infections

Among nonparasitic pathogens, fungi can provoke pulmonary eosinophilia through hypersensitivity responses. Coccidioidomycosis, caused by *Coccidioides immitis* and *Coccidioides posadasii*, is acquired *via* inhalation of spores in the southwestern United States, Mexico, and parts of Central and South America and frequently features eosinophilia, with peripheral eosinophilia in up to 88% of acute infections.[35,36] Patients may have fever, cough, and erythema nodosum. Radiographic features, such as consolidation, nodules, and pleural effusions, are common.[37,38] Paracoccidioidomycosis, found in Latin America with highest endemicity in Brazil, may produce a similar pattern of peripheral and pulmonary eosinophilia, particularly in children and adolescents during the acute phase. In both infections, serologic assays have variable performance, whereas histopathology or culture provides definitive diagnosis. Eosinophilia has been associated with disease severity, but it typically resolves with appropriate antifungal therapy.[38,39]

Aspergillus species are ubiquitous environmental molds classically associated with ABPA rather than invasive disease.[40] However, invasive and disseminated aspergillosis rarely present with marked eosinophilia; in such cases, the eosinophilia likely reflects a concomitant hypersensitivity to fungal antigens in a susceptible host rather than a hallmark of dissemination.[41-44] When eosinophilia accompanies suspected invasive or disseminated Aspergillus, histopathology and culture, galactomannan, and imaging should be performed. Concurrent ABPA or other hypersensitivity should be assessed, and clinicians should exercise caution with empiric glucocorticoids until invasion is excluded.[45]

Bacterial and viral causes

Bacterial infections are uncommon causes of pulmonary eosinophilia. A notable exception is infant *Chlamydia trachomatis* pneumonia, which can cause peripheral eosinophilia in the setting of an afebrile illness with "staccato cough."[46] In adults, alveolar eosinophilia that improves with therapy has been described occasionally in *Mycobacterium avium* lung disease.[47,48] In tuberculosis, similar cases have been reported, and eosinophils have repeatedly been shown to be present within tuberculous granulomata.[49,50] However, a prominent eosinophilic infiltrate in the setting of tuberculosis should prompt investigation into other etiologies.[51]

Viral pathogens can modestly increase BAL eosinophilia, but frank eosinophilic pneumonia is uncommon. In a retrospective series of lower respiratory tract viral infections, PCR-positive cases (parainfluenza, influenza A, respiratory syncytial virus, rhinovirus, human metapneumovirus) showed mild increases in BAL eosinophilia, with 2 of 17 infectious BAL specimens meeting criteria for eosinophilic pneumonia, both due to parainfluenza. Scattered case reports document AEP temporally associated with recent severe acute respiratory syndrome coronavirus 2 infection, though the dominant phenotype in acute infection is eosinopenia.[52-55] Prominent pulmonary eosinophilia, particularly when accompanied by systemic features such as rash and fever, should not be attributed to viral or bacterial infection without a thorough workup for other etiologies including medications, parasitic infection, and autoimmune and neoplastic disease.

ALLERGIC AND AIRWAY DISEASES

Allergic bronchopulmonary aspergillosis

ABPA is an airways disease that occurs because of an exuberant, complex hypersensitivity reaction to Aspergillus antigens.[56,57] In general, ABPA does not occur in the setting of a pulmonary Aspergillus infection, but rather in response to colonization of the airways by this ubiquitous mold. Asthma and cystic fibrosis are common predisposing conditions for ABPA; however, ABPA can also occur in patients with bronchiectasis without a previous history of asthma or cystic fibrosis.[58] Type 2 immune responses to Aspergillus antigen are characteristic of ABPA, with blood eosinophilia often observed, leading to the categorization of ABPA as an eosinophilic lung disease. However, hypereosinophilia is rarely present in ABPA. Patients usually have some evidence of bronchiectasis on chest imaging, with central bronchiectasis and evidence of mucous plugging as particularly distinctive finding in many cases.[59] ABPA is classically associated with asthma or cystic fibrosis, but these conditions are not mandatory in all cases, particularly among patients with bronchiectasis.[60,61] Accordingly, current guidelines recommend evaluation for ABPA in patients with bronchiectasis when clinical features are compatible.[60] There must also be evidence of allergic sensitization to Aspergillus antigen by either the presence of specific IgE to Aspergillus on serologic testing or by skin testing. Total IgE levels are usually very high in ABPA, often exceeding 1.000 IU/mL, though lower levels may be seen in some individuals. Other diagnostic criteria include the presence of blood eosinophilia (often $>0.5 \times 10^9$/L as a supportive feature), chest imaging findings consistent with ABPA, and elevated specific IgG to *A fumigatus*. ABPA is part of a broader spectrum of allergic bronchopulmonary mycoses, in which similar clinical, radiologic, and immunologic features may be caused by non-Aspergillus fungi. In such cases, Aspergillus-specific IgE may be negative, and diagnosis relies on

compatible clinical features, elevated total IgE, and evidence of fungal sensitization.[60] Patients are usually treated with inhaled therapies for underlying asthma, such as inhaled glucocorticoids and long-acting beta agonists. In most patients, initial treatment consists of a course of systemic glucocorticoids, which remain the cornerstone of therapy for controlling acute disease activity and preventing progression of bronchiectasis. Courses of antifungal azole agents may be administered to reduce the antigenic burden of Aspergillus in the airways.[62] mAbs against targets involved in type 2 inflammation are increasingly being used, with a recent randomized trial showing efficacy in ABPA of the anti−IL-4-receptor-alpha agent dupilumab.[63]

Acute eosinophilic pneumonia

AEP is a rapidly progressive ELD characterized by acute febrile illness, hypoxemic respiratory failure, and diffuse pulmonary infiltrates. Peripheral blood eosinophilia may be absent at presentation, whereas BAL typically demonstrates marked eosinophilia.[1] AEP is frequently associated with recent exposures, including initiation or resumption of cigarette smoking, inhalational exposures, or medications. Prompt recognition is essential, because patients usually show a dramatic response to systemic glucocorticoids.

Chronic eosinophilic pneumonia

CEP is a condition characterized by the presence of eosinophils in the lung parenchyma, both alveolar spaces and interstitium, on the background of elevated blood eosinophils.[57] As the name implies, CEP is chronic, developing over the course of months to years with progressive and episodic dyspnea and hypoxemia. Systemic symptoms, such as fatigue and night sweats, may occur as well. Because CEP can often occur in patients with antecedent asthma, repeated courses of systemic glucocorticoids may have been given before a diagnosis is made. Pulmonary infiltrates are generally always present in CEP, though may wax and wane depending on the presence of concurrent systemic glucocorticoids. The infiltrates have been classically described as peripheral, invoking the description of being the "photographic negative of congestive heart failure."[64] However, patterns of air-space opacity may vary from this classic description.[9,65] Bronchoscopy with BAL will show elevated eosinophils on differential cell count.[9] CEP responds very well to systemic glucocorticoids, though patients may have refractory symptoms with attempts to taper and prolonged courses of several months may be needed. The pathogenesis of CEP is incompletely understood, but is thought to reflect a dysregulated type 2 immune response with eosinophilic infiltration of the alveolar spaces and interstitium. Importantly, CEP remains a diagnosis of exclusion and requires careful exclusion of secondary causes of pulmonary eosinophilia, including infections, drug reactions, and systemic diseases.[65]

Asthma-associated pulmonary eosinophilia

Since the observation of the presence of the Charcot-Leyden crystals in the sputum of patients with asthma with the advent of microscopy in the 19th century, there has long been an association noted between eosinophils and asthma.[66] In the early 20th century, autopsy specimens from patients with fatal asthma demonstrated eosinophilic infiltration of the airways.[67] Although the strong link between eosinophils and many patients with asthma had been well established, it has only been more recently over the last 2 decades that the mechanistic importance of eosinophils in type 2−high asthma has been definitively demonstrated with both animal studies and robust clinical efficacy data of eosinophil-depleting agents targeting IL-5 or its receptor.[68-73] Another critical development in asthma has been the emergence of blood and sputum eosinophilia as biomarkers for predicting the likelihood of response to inhaled and systemic glucocorticoids, anti−IL-5/IL-5R biologics, and other type 2−targeting biologics, such as anti−IL-4-Ra, anti−thymic stromal lymphopoietin, anti-IgE, and other agents in clinical development.[74-78] Although sputum eosinophils are more directly reflective of the presence of eosinophils in the airways, blood eosinophil counts are more commonly used in clinical practice given lower operational barriers to obtaining a measurement. Although blood eosinophils do act as a continuous variable in predicting response to asthma therapies, 300 cells per microliter is a critical cutoff point that is often used as a predictive biomarker for the use of eosinophil-depleting biologics.[79] Recently, there has been emerging interest in blood eosinophils as a biomarker of risk of future exacerbation, even in patients who may have been under adequate control of their asthma.[80,81]

Overlap with other entities

There are overlaps between these allergic and airway ELDs and other eosinophil diseases. There is significant overlap between severe asthma, CEP, and some presentations of EGPA, which are discussed in more detail below. Indeed, almost all patients with EGPA have antecedent asthma, which often predates the onset of systemic disease and extrapulmonary manifestations by several years.[14] By EGPA classification criteria used in clinical trials, many patients with CEP would come close to meeting criteria for antineutrophil cytoplasmic antibody (ANCA)-negative disease based on concurrent asthma, elevated blood eosinophilia, and pulmonary infiltrates.[3] These observations suggest that severe eosinophilic asthma, CEP, and ANCA-negative EGPA may lie on the same spectrum of disease. Similarly, hypereosinophilic syndrome (HES) with pulmonary involvement also overlaps with CEP given the shared features of systemic eosinophilia and pulmonary infiltrates. AEP and CEP have the presence of BAL eosinophilia and pulmonary infiltrates as common features, though AEP tends to be much more rapid in onset, be associated with severe respiratory failure, and lacks the presence of blood eosinophilia at presentation.[57] Eosinophilia may also be observed in other chronic airway diseases, highlighting the need for careful differential diagnosis.[82]

HESs: Diagnostic and clinical implications

HESs include a range of diseases characterized by persistent hypereosinophilia (HE; ie, an absolute eosinophil count in peripheral blood $\geq$1500 cells/μL, confirmed on at least two occasions $\geq$2 weeks apart) associated with organ damage caused by eosinophils.[15] HES includes lymphocytic-variant HES (L-HES), clonal myeloid HES (M-HES), and idiopathic HES (i-HES). Clinically significant organ damage from eosinophil activity may include fibrosis (affecting the lungs, heart, or digestive tract), thrombosis, skin lesions, neuropathy affecting the central or peripheral nervous system, and involvement of other organs such as lung, liver, pancreas, or kidneys.[83] Signs and symptoms tend to overlap across different HES categories. In a recent article by Requena et al,[16] among respiratory symptoms at presentation, the most common were dyspnea/shortness of breath and cough reported in 14.4% and 12.4% of all HES

cases, and in 21.1% and 14.5% of i-HES cases. In addition, lung and pulmonary abnormalities, pleural effusion, and asthma were respectively reported in 10.5%, 4.6%, and 2.6% of i-HES cases, whereas they were less frequently reported in L-HES and M-HES. Considering organ involvement both at presentation and/or during the disease course, lung was affected in 33.6%, 23.3%, and 19.4% of i-HES, M-HES, and L-HES cases, respectively.[16] Pulmonary abnormalities on radiologic studies have been described in 14% to 28% of patients with HES and consisted of nodules, ground-glass opacities, interlobular septal thickening, and pleural effusion; however, it was unclear whether the intrathoracic findings were directly attributable to eosinophilic infiltration or not.[84,85] In a Mayo Clinic study including 11 i-HES cases and 1 L-HES case, radiologic features most consisted of a combination of ground-glass opacities and consolidation in a patchy distribution.[86]

Lymphocytic-variant HES

L-HES is a rare reactive cause of HES, defined by the presence of a clonal population of T lymphocytes in peripheral blood and/or rearrangement of the T-cell receptor. The most common immunophenotype of the aberrant population is $CD3^{-}CD4^{+}$, but other populations such as $CD3^{+}CD4^{-}CD8^{-}$ and $CD4^{+}CD7^{-}$ have been reported, leading to the overproduction of T_H2 cytokines as IL-4, IL-5, and IL-13. Increased serum levels of immunoglobulins, mainly IgE, is also characteristic. L-HES is characterized by an increased risk of developing lymphoproliferative neoplasm mainly as angioimmunoblastic T-cell lymphoma.[87] Lymphoproliferative disorders that may present with HE, aberrant T-cell immunophenotype, and overlapping clinical features with L-HES include IgG4-related disease, cutaneous T-cell lymphomas, and peripheral T-cell lymphomas as angioimmunoblastic T-cell lymphoma. Workup to exclude these conditions may include cross-sectional imaging, tissue biopsy, and peripheral blood flow cytometry. Patients with L-HES frequently present with cutaneous manifestations, and additional organ involvement may include bone marrow, lymph nodes, lungs, and spleen.[16,88] Glucocorticoids are generally the first treatment option, but for patients who do not respond or relapse, alternatives such as anti−IL-5/IL-5R therapy (eg, mepolizumab or benralizumab), pegylated IFN-α, and Janus kinase inhibitors should be considered.[89]

Clonal myeloid HES

In cases of HE associated with hematopoietic neoplasms, eosinophils frequently exhibit identical molecular genetic aberrations as their progenitor cells and/or other clonal myeloid populations. According to the 2022 World Health Organization classification[90] and International Consensus Classification of myeloid neoplasm,[91,92] these hematopoietic neoplasms are classified into 3 categories: (1) HE concomitant with other defined myeloid malignancies, such as chronic myeloid leukemia or acute myeloid leukemia with chromosome 16 inversion; (2) myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (M/LN-Eo-TK); and (3) chronic eosinophilic leukemia, not otherwise specified. In most of these cases, peripheral blood smears reveal immature cells of the myeloid lineage and/or dysplastic eosinophils.[93] The clinical manifestations of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase mutations (M/LN-Eo-TK) vary widely.[16] *PDGFRA* rearrangements are the most frequent genetic abnormality in M/LN-Eo-TK, followed by *PDGFRB*; several other tyrosine kinase fusions, including *FGFR1, JAK2, FLT3,* and *ABL1*, have also been described.[94] Concerning treatment, *FIP1L1::PDGFRA* and most *PDGFRB*-rearranged cases aresensitive to imatinib 100 to 400 mg daily; pemigatinib is effective in many *FGFR1* rearranged cases, whereas ruxolitinib may be an option in *JAK2* cases.[95] Chronic-phase *PDGFRA*- and most *PDGFRB*-rearranged diseases have a favorable prognosis, whereas blast-phase disease and other rearrangements carry poorer outcomes and may require allogeneic hematopoietic stem cell transplantation.[96,97] Chronic eosinophilic leukemia, not otherwise specified is an exceptionally rare myeloid neoplasm characterized by an increased population of blast cells in the peripheral blood and/or bone marrow and/or the demonstration of clonal eosinophils in cytogenetic or molecular analysis. Splenomegaly and signs/symptoms of myocardial and pulmonary involvement are most frequently observed.[16] Recently, activating mutations in *JAK1*[98] and *STAT5B*[99] have been described. Hydroxyurea, pegylated IFN-α, or conventional chemotherapy are used; however, allo-HSCT should be considered.[97]

Idiopathic HES

i-HES remains a diagnosis of exclusion, with a normal morphology of bone marrow except for HE, and no evidence of clonality.[92] At diagnosis, patients with i-HES presented frequently with cardiac left ventricular abnormalities/murmur/thrombus (22.4%) and respiratory symptoms such as dyspnea (21.1%), cough (14.5%), or lung and pulmonary abnormalities (10.5%). During disease course, a wide spectrum of clinical manifestations in i-HES are reported, mainly related to heart (34.9% of patients), bone marrow (34.9%), and lung (33.6%).[16] ANCA-negative EGPA shares many features with i-HES, which makes it difficult to distinguish between the 2 conditions. Both have similar demographic patterns, clinical symptoms, glucocorticoid maintenance needs, and cytokine profiles. However, i-HES can often be identified by its lower rate of asthma and lack of sinus involvement.[14,17] Glucocorticoids remain the primary treatment for i-HES, helping to reduce eosinophil count and control symptoms. Recently, a phase III trial confirmed that anti−IL-5 mepolizumab at 300 mg every 4 weeks is an effective and safe glucocorticoid-sparing therapy, significantly reducing flares.[18] Other options include anti−IL-5R benralizumab.[19]

AUTOIMMUNE AND SYSTEMIC INFLAMMATORY DISEASES

In the context of ELDs, autoimmune and systemic inflammatory disorders represent a key category in which pulmonary involvement may either dominate the clinical picture or occur as part of multiorgan disease. Among these, EGPA is the prototypical condition. However, connective tissue diseases (CTDs) and HES can also manifest with pulmonary eosinophilia and should be considered in the differential diagnosis.

Epidemiology and clinical context

EGPA is a rare small-vessel vasculitis characterized by asthma, peripheral and tissue eosinophilia, and necrotizing granulomatous inflammation involving the respiratory tract and other organs.[4] The respiratory system is nearly always affected,

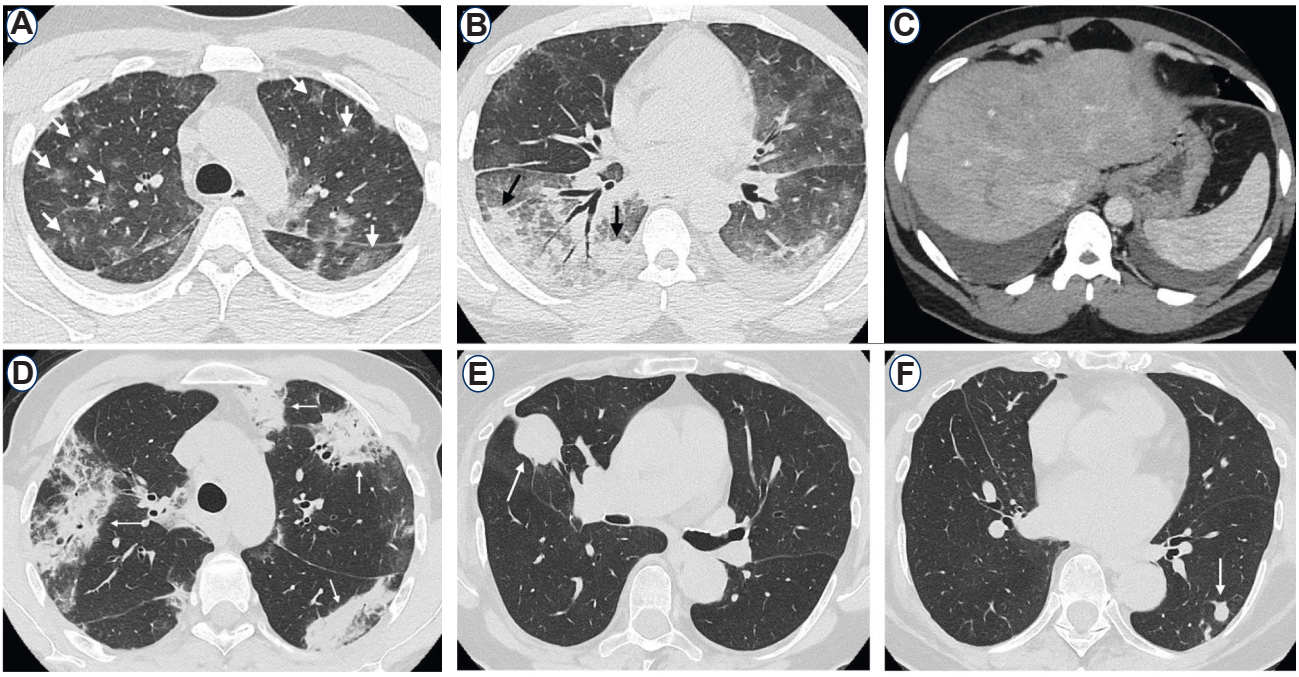

FIGURE 2. Representative chest CT images from different eosinophilic lung disorders. (**A, B, C**) *AEP*. High-resolution CT images on the axial plane demonstrate the presence of diffuse patchy bilateral ground-glass opacity (white arrows) and air-space consolidation in the lower right lobe (black arrows) (Figure 2, *A* and *B*). After contrast media administration, a bilateral pleural effusion is more clearly visible in the posterior basal regions (Figure 2, *C*). (**D, E, F**) *CEP*. High-resolution CT scan demonstrates typical nonsegmental areas of bilateral air-space consolidation with peripheral predominance (white arrows) (Figure 2, *D*), with a middle or upper zone predilection; *Mass-like nodules*. Chest CT demonstrates the presence of a mass-like lesion in the upper right lobe (Figure 2, *E*) and a nodule in the lower left lobe (Figure 2, *F*) (white arrows).

encompassing upper-airway disease, chronic asthma, and pulmonary infiltrates of variable morphology. In a multicenter French Vasculitis Study Group cohort of 157 patients, pulmonary abnormalities were present in all cases, with high-resolution computed tomography (HRCT) showing transient and migratory opacities in more than 50%.[5]

ANCAs are detectable in approximately one-third of patients and correlate with a vasculitic phenotype, whereas ANCA-negative patients more often exhibit eosinophilic organ infiltration.[1,6] Importantly, lung-dominant disease can occur irrespective of ANCA status.[7]

Beyond EGPA, a spectrum of other autoimmune and systemic inflammatory disorders may feature pulmonary involvement associated with eosinophilic or mixed inflammatory infiltrates. Although less common, such manifestations are increasingly recognized across CTDs and granulomatous disorders, may significantly influence prognosis and treatment response, and must be included in the diagnostic evaluation.[1]

Systemic lupus erythematosus can occasionally manifest with pulmonary eosinophilia, as part of acute lupus pneumonitis, organizing pneumonia, or drug-induced eosinophilic pneumonia triggered by immunosuppressants or antibiotics.[100-104] Histologically, alveolar and interstitial eosinophilic infiltrates can coexist with immune complex deposition and capillaritis.[101,105,106] Reports suggest that eosinophilic inflammation may precede full-blown lupus pneumonitis and is usually highly glucocorticoid-responsive, with complete radiologic resolution in most cases.[9,100,102-104,107] Differentiation from EGPA relies on the absence of asthma, ANCA negativity, and the presence of typical lupus serology (ie, ANA, anti—double-stranded DNA, anti-Sm).[1,13,108-110]

Systemic sclerosis—related interstitial lung disease (ILD) is typically fibrotic (predominantly nonspecific interstitial pneumonia), but eosinophilic BAL profiles are observed in up to one-third of cases, reflecting T_H2-skewed inflammation and epithelial-fibroblast crosstalk.[111-115] In some patients, an eosinophilic pneumonitis-like pattern or organizing pneumonia (OP) may occur, either spontaneously or during treatment with some drugs.[116,117] Recognition of this inflammatory component is important because early glucocorticoid or mycophenolate mofetil (MMF) therapy can reduce progression to fibrosis and improve functional outcomes.[118-120]

Rheumatoid arthritis can also present with eosinophilic pulmonary involvement, most often in the context of rheumatoid arthritis—associated ILD or drug-induced pneumonitis (particularly after methotrexate or leflunomide exposure).[121,122] A subset of patients develops eosinophilic pneumonia independently of drug exposure, with BAL or biopsy showing interstitial eosinophilia and OP features.[123,124] As in systemic sclerosis, this inflammatory subtype tends to respond favorably to glucocorticoids or steroid-sparing immunosuppressants such as azathioprine or rituximab.[1,125-128]

Sarcoidosis, although classically associated with noncaseating granulomatous inflammation rather than eosinophilia, may

rarely display prominent eosinophilic alveolitis or peripheral blood eosinophilia.[129-132] This pattern has been described in active pulmonary disease, possibly reflecting T_H2/IL-5 pathway activation or overlapping hypersensitivity reactions.[133,134] BAL eosinophilia exceeding 5% in sarcoidosis has been linked with disease activity and may predict a better response to systemic glucocorticoids.[135,136]

Collectively, these autoimmune and granulomatous conditions highlight that pulmonary eosinophilic or mixed-cell inflammation is not pathognomonic of EGPA. Instead, it may represent an epiphenomenon of immune dysregulation, drug exposure, or fibrosing ILD with an inflammatory component. Integrating HRCT, BAL cytology, and serologic profiling allows distinction between primary ELDs and secondary eosinophilic inflammation within systemic autoimmune disorders. Importantly, early recognition of eosinophilic alveolitis in CTD or sarcoidosis may prompt timely initiation of glucocorticoids or immunomodulatory therapy (MMF, azathioprine, or rituximab), thereby preventing irreversible fibrotic remodeling and optimizing long-term pulmonary outcomes.

Pathophysiology and immunologic mechanisms

ELDs share overlapping immunopathogenic mechanisms centered on type 2—skewed inflammation, with variable contributions from eosinophilic tissue infiltration, epithelial injury, and, in selected conditions, immune-mediated vasculitis. Across ELDs, key drivers include IL-5—dependent eosinophil expansion and survival, epithelial-derived alarmins such as IL-33 and thymic stromal lymphopoietin, and activation of T_H2 T cells and innate lymphoid cells. The relative contribution of these pathways varies among idiopathic eosinophilic pneumonias, allergic airway diseases, HES, and autoimmune conditions. Within the spectrum, the immunopathogenesis of EGPA involves a dual process of T_H2-driven eosinophilic inflammation and small-vessel vasculitis. Eosinophils release toxic granule proteins (eg, major basic protein, eosinophil cationic protein, and eosinophil peroxidase) that damage endothelium and parenchyma.[8] Cytokines including IL-5, IL-4, and IL-13 orchestrate eosinophil recruitment and activation, whereas type 2 innate lymphoid cells further amplify tissue inflammation.[137] Recent single-cell transcriptomic studies have identified distinct inflammatory endotypes in EGPA, with ANCA-positive cases enriched for neutrophil and B-cell signatures, and ANCA-negative cases showing eosinophil and T_H2 predominance.[138] These findings help explain the variability in pulmonary injury patterns and therapeutic responses. In the lung, eosinophilic infiltration may precede or accompany vasculitic lesions, producing a spectrum from OP to necrotizing granulomatous inflammation.

Pulmonary manifestations and imaging features

Pulmonary involvement in autoimmune eosinophilic disorders displays a wide spectrum of radiologic patterns that reflect underlying pathology, ranging from simple eosinophilic infiltration to alveolar damage, OP, or hemorrhage.

In EGPA, transient or migratory air-space opacities, ground-glass attenuation, and patchy consolidations are characteristic and often peripheral or subpleural in distribution.[108] Nodular lesions, occasionally cavitating, may reflect vasculitic necrosis, while pleural effusions are seen in up to 30% of cases.[5] A comprehensive review of HRCT features of ELDs by Bernheim and McLoud[108] highlighted that peripheral consolidation, ground-glass opacities, and "crazy-paving" are the most suggestive imaging clues for eosinophilic pneumonia patterns. In the setting of vasculitis, diffuse alveolar hemorrhage may occur, albeit less frequently than in microscopic polyangiitis; HRCT typically shows diffuse bilateral ground-glass opacities or consolidations with interlobular septal thickening.[8] An OP-like pattern, characterized by subpleural consolidations with air bronchograms, can also be observed and is thought to represent eosinophil-driven alveolar injury rather than true vasculitic infarction[4] (Figure 2).

Diagnostic considerations

The heterogeneity of pulmonary imaging findings in autoimmune ELD mandates a high index of suspicion. The diagnostic triad of adult-onset asthma, blood or BAL eosinophilia, and systemic vasculitis should prompt targeted evaluation for the exclusion of EGPA. HRCT revealing nonfixed or migratory opacities strongly supports an eosinophilic process.[1] Laboratory workup should include eosinophil count, total IgE, ANCA testing, and evaluation of other organ involvement (eg, cardiac MRI, nerve conduction studies, and renal function). BAL eosinophilia higher than 5% is suggestive of ELD; however, BAL may be nondiagnostic in selected conditions, and lung biopsy should be considered when clinical suspicion remains high, particularly to document vasculitis, fibrosis, or alternative diagnoses.

Differentiating eosinophilic-predominant inflammation from other ILDs associated with CTDs is crucial, because management strategies differ markedly. For instance, in CTD-associated ILD with eosinophilia, early glucocorticoid or immunosuppressive therapy (MMF or azathioprine) may prevent irreversible fibrosis.[10] Recent international consensus recommendations for EGPA stress the role of HRCT, BAL, and tissue biopsy in diagnostic algorithms and underscore the need for close collaboration among pulmonologists, rheumatologists, and radiologists.[13]

Therapeutic and prognostic implications

Recognition of pulmonary eosinophilic involvement in autoimmune diseases has direct therapeutic consequences. Glucocorticoids remain the cornerstone of therapy, typically inducing rapid improvement in both respiratory and systemic manifestations.[4] The introduction of anti—IL-5 biologics (ie, mepolizumab and benralizumab) has revolutionized treatment, reducing relapse frequency and glucocorticoid dependence in EGPA.[3] In refractory or relapsing disease with vasculitic features, adjunctive immunosuppressants (azathioprine, methotrexate, cyclophosphamide) or biologics targeting B cells (rituximab) may be required.[1]

From a pulmonary perspective, early recognition of eosinophilic infiltration allows timely glucocorticoid initiation, reduces the risk of relapse, and prevents chronic fibrotic remodeling. HRCT monitoring is recommended to assess treatment response and detect subclinical recurrence. Prognosis in EGPA has improved markedly, with 5-year survival exceeding 90%, yet lung involvement remains a major determinant of morbidity.[5] Persistent or recurrent infiltrates should prompt evaluation for incomplete disease control or evolution toward fibrotic ILD.

For systemic diseases with eosinophilic lung involvement beyond EGPA, management principles remain similar but must

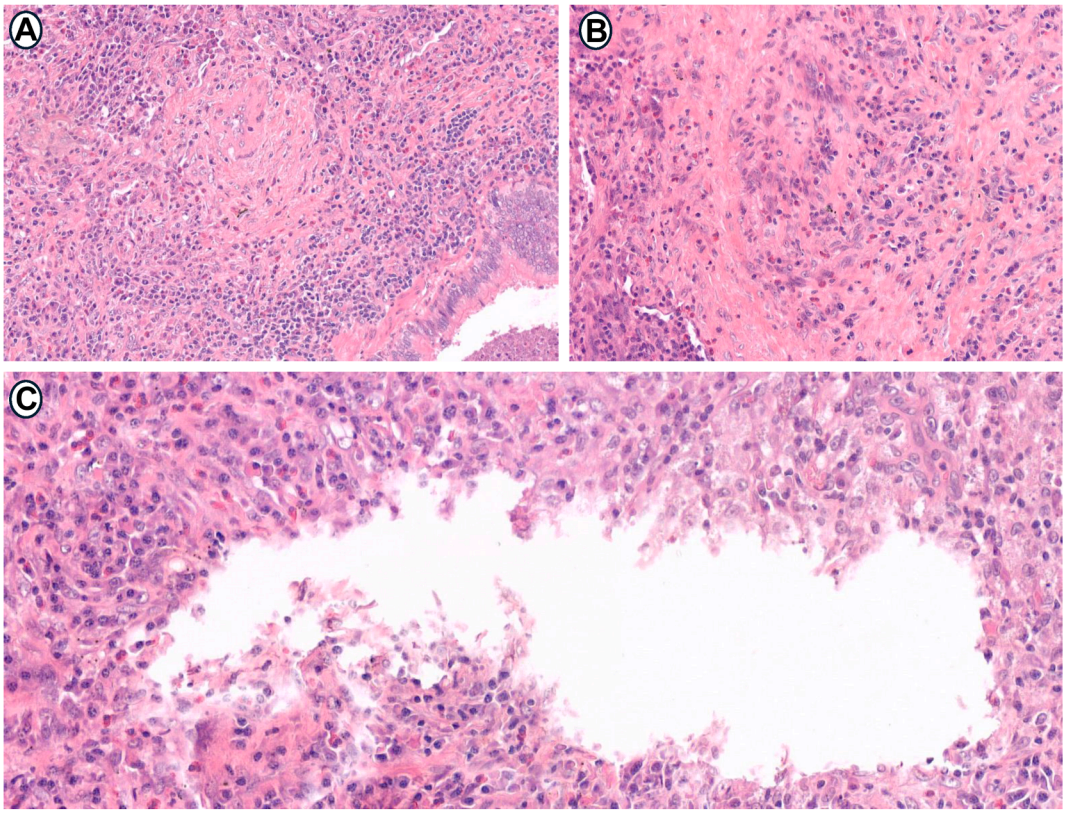

FIGURE 3. Histopathologic features of eosinophilic lung disease in a patient with EGPA. (**A**) Necrotizing eosinophilic granuloma with a pale, fibrous-necrotic center. The surrounding inflammatory rim contains irregularly distributed epithelioid histiocytes, numerous eosinophils, and scattered lymphocytes and plasma cells. (**B**) Fibrinoid necrosis bordered by a mixed inflammatory infiltrate rich in eosinophils and epithelioid histiocytes, forming a necrotizing eosinophilic granulomatous reaction. The adjacent parenchyma is remodeled, with loss of alveolar architecture. (**C**) Dense eosinophilic infiltrate involving the vessel wall, with a prominent, dilated vascular lumen centrally visible. The wall shows discontinuity and fibrinoid change, accompanied by eosinophils, lymphocytes, and macrophages. The surrounding parenchyma is effaced by eosinophil-rich inflammation. Histopathologic images courtesy of Dr Francesco Ferro (University of Pisa, Italy).

be tailored to the underlying pathobiology. In CTD-associated eosinophilic ILD, eosinophilic inflammation may coexist with fibrotic patterns such as nonspecific interstitial pneumonia or OP, and its recognition can influence treatment decisions.[11,139] Early glucocorticoid therapy combined with corticosteroid-sparing immunosuppressants, typically MMF or azathioprine, may stabilize or reverse parenchymal abnormalities, whereas delayed diagnosis can lead to irreversible fibrosis.[140,141]

Diagnostic algorithms and practical approach

The diagnostic evaluation of ELDs requires a structured, stepwise approach aimed at confirming eosinophilic involvement, identifying secondary causes, and characterizing systemic associations. Because radiologic, serologic, and clinical features often overlap, a multidisciplinary strategy involving pulmonologists, allergists, rheumatologists, radiologists, and oncohematologists is essential.

The first diagnostic step is to confirm the presence of eosinophilia. Peripheral blood eosinophilia ($\geq$500 cells/μL) suggests an eosinophilic process, but is not mandatory for diagnosis. When eosinophilia is absent or modest, BAL remains the most sensitive method to demonstrate pulmonary eosinophilic infiltration. In healthy individuals, eosinophils typically account for less than 1% to 2% of BAL cells, whereas values exceeding 5% are considered abnormal and, in the appropriate clinical context, strongly suggest ELD.[12,118] Quantitative BAL analysis also assists in differentiating eosinophilic disorders from other ILDs or infections.

Once eosinophilia is confirmed, secondary causes must be systematically excluded. Infectious etiologies, including helminthic and fungal infections, should be ruled out through stool examination, serologic testing, and culture. Drug-induced eosinophilic pneumonia should be considered in all patients with recent exposure to antibiotics, nonsteroidal anti-inflammatory drugs, or biologics.[12,13] Additional evaluation should include screening for ABPA, hematologic malignancies (in particular HES), and systemic autoimmune disorders (especially EGPA). HRCT is crucial to characterize the pattern of lung involvement. Certain features are particularly informative; for example, peripheral consolidations suggest CEP, diffuse ground-glass opacities indicate AEP or diffuse alveolar hemorrhage, while nodular or less frequently cavitary lesions may raise

suspicion for EGPA or HES.[108] When imaging and laboratory data remain inconclusive, lung biopsy may be required to distinguish between eosinophilic infiltration, vasculitis, or neoplastic processes (Figure 3).

The third step is to assess for systemic disease. ANCA testing, cardiac evaluation, and molecular studies (eg, FIP1L1-PDGFRA) guide differentiation between autoimmune and clonal eosinophilic syndromes. Integrating these findings usually allows clinicians to classify patients into idiopathic (AEP, CEP) *versus* secondary forms, with direct therapeutic implications.

A practical diagnostic algorithm is proposed (Figure 1), beginning with eosinophilia confirmation (blood or BAL), exclusion of secondary causes, and tiered evaluation for systemic involvement before diagnosing idiopathic eosinophilic pneumonia. This structured pathway supports timely recognition and treatment of ELDs, reducing unnecessary immunosuppression and improving outcomes.[1]

Conclusion and future perspectives

ELDs encompass a broad and heterogeneous *spectrum* in which accurate diagnosis relies on systematic integration of clinical, radiologic, and laboratory data. Despite advances in imaging and molecular testing, diagnostic uncertainty remains frequent, especially in distinguishing idiopathic from secondary causes. The implementation of algorithmic diagnostic pathways and multidisciplinary evaluation has proven essential to improve accuracy and avoid delays in appropriate therapy. Recent developments in targeted biologic therapies, particularly IL-5 and IL-5R antagonists such as mepolizumab and benralizumab, have transformed management of eosinophilic disorders, including EGPA and selected hypereosinophilic syndromes.[3,142-145] However, most evidence derives from small, heterogeneous cohorts, and biomarkers predictive of response or relapse remain limited. Future research should prioritize standardized diagnostic criteria, longitudinal registries, and molecular profiling to better define disease subsets and therapeutic responses. Ultimately, improving recognition of ELDs demands close collaboration between specialties, integration of advanced imaging and omics-based approaches, and validation of clinical algorithms in prospective studies. Such efforts will refine diagnosis, personalize treatment, and improve long-term outcomes for patients with ELDs.

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