Eosinophilic lung diseases: A review

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The terms 'eosinophilic pneumonia' and 'eosinophilic lung disease' loosely describe a heterogeneous group of pulmonary diseases of varying aetiologies and severity. The diseases are characterised by infiltration of lung parenchyma by eosinophils; peripheral eosinophilia is not required for diagnosis. In this article, major clinical entities are appraised with respect to clinical, pathological and radiological features. Diseases without pulmonary infiltration or radiographic abnormalities, such as allergic asthma, are not included in this review.

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There are several recognised clinical and radiographic presentations of eosinophilic lung disease. These include simple pulmonary eosinophilia (SPE), chronic eosinophilic pneumonia (CEP), acute eosinophilic pneumonia (AEP), allergic bronchopulmonary aspergillosis (ABPA) and pulmonary eosinophilia associated with a systemic disease.[1] Systemic diseases implicated include eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome (CSS) and the hypereosinophilic syndrome (HES). Eosinophilic pneumonias may be idiopathic or secondary to a known cause. Causes may include drugs, irradiation, toxins and infections. The infections may be fungal, parasitic or mycobacterial in nature. AEP, CEP and ABPA have radiographic features that may be suggestive, if not pathognomonic, in several instances. In addition, varying degrees of pulmonary eosinophilia may be associated with diffuse lung diseases, neoplasia and connective tissue diseases. Finally, a hallmark of eosinophilic lung diseases (with the exception of HES) is their exquisite sensitivity to corticosteroids.

The eosinophil leukocyte is of obvious importance. It is a granulocyte named for its abundance of eosinophilic granules in the cytoplasm. Mature eosinophils circulate for approximately 24 hours before being recruited into target tissues where they undergo rapid apoptosis if no survival factors are present.[2] Recent studies have suggested a role for eosinophils apart from that of end-stage anti-parasitic cells. These include roles in both innate and adaptive immunity, including antigen presentation to Th2 cells and other interactions with mast and T cells.[3] Eosinophils release several toxic substances from the small and large granules in their cytoplasm that are thought to contribute to the pathophysiology of these diseases. The smaller granules contain the characteristic cationic proteins: major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and eosinophil peroxidase (EPO).[4]

General concepts

Disorders may be classified as eosinophilic lung disease in one of three ways:[5]

1. **Peripheral blood eosinophilia and radiographic infiltrates** (pulmonary infiltrates with eosinophilia or PIE syndrome). Is it important to note that blood eosinophilia does not prove lung eosinophilia and that lung involvement is not invariably accompanied by blood eosinophilia. The absolute eosinophil count is preferred over the percentage. A normal blood eosinophil count ranges from 50 to 250 cells/μL.[5]
2. **Lung biopsy.** This can be accomplished by the transbronchial route or open lung biopsy. Open lung biopsy is considered the 'gold standard' because it yields adequate amounts of alveolar and vascular tissue. Histological findings are remarkably consistent across all forms of these diseases and include an intra-alveolar and interstitial exudate of histiocytes and eosinophils, eosinophilic microabscesses, and findings of an organising pneumonia. There may be small areas of interstitial necrosis and fibrosis. A small degree of vasculitis is allowed, as long as granulomata are absent. Frank eosinophilic vasculitis is indicative of EGPA and granulomata are found in parasitic infections, EGPA and ABPA.[1]
3. **Bronchoalveolar lavage (BAL).** This technique has several advantages in that it is minimally invasive, safe and can be used to monitor response to therapy. Eosinophilia is defined as >5%, severe eosinophilia as >25%.[6]

Classification

There is no widely accepted classification of the eosinophilic lung diseases. Table 1 suggests a classification in terms of clinical and radiological presentation and aetiology.[1,5] Table 2 describes the infectious causes of pulmonary eosinophilia and the primary mechanism whereby they exert their effects. A detailed review of the infectious causes is not possible due to space constraints. Drugs are another major cause of pulmonary eosinophila. Non-steroidal anti-inflammatory drugs, immunosuppressants and antibiotics are most commonly implicated. A comprehensive list is available at www.pneumotox.com.

Eosinophilic lung diseases

Simple pulmonary eosinophilia

In 1932, Wilhelm Löffler described a syndrome of migratory pulmonary infiltrates with peripheral eosinophilia and minimal pulmonary symptoms.[7] In his original series, most cases were due to *Ascaris* infection. The term is now used more broadly to describe

SPE resulting from any fungal, parasitic or drug-induced cause. The transient nature of eosinophilic pulmonary infiltrates and symptoms mirror the transpulmonary passage of larvae in the lifecycle of parasites including *Ascaris*,[7] hookworms such as *Ancylystoma duodenale* or *Nector americanus* and *Schistosoma* spp.[7] Though most patients remain minimally symptomatic, 8 - 15% display respiratory symptoms such as wheeze, cough and haemoptysis approximately 9 - 12 days post ingestion of eggs. Symptoms may last 5 - 10 days; severity correlates with worm burden. If required, a definitive diagnosis may be made by recovery of larvae via respiratory secretions and gastric lavage fluid. Eggs will be detectable in stools 14 days after ingestion.

The radiographic pattern often consists of patchy peripheral infiltrates with a pleural base. Coalescence may occur in severe cases. Spontaneous resolution of the syndrome within 30 days is the norm and therapy is rarely required. Corticosteroids have been used successfully in severe cases.[9]

Importantly, transient radiographic infiltrates occur in other forms of eosinophilic lung disease, including ABPA, EGPA and HES.

Table 1. Classification of pulmonary eosinophilia[1]

Principal forms of pulmonary eosinophilia (based on clinical and radiological presentation)
1. Simple pulmonary eosinophilia
2. Chronic eosinophilic pneumonia
3. Acute eosinophilic pneumonia
4. Allergic bronchopulmonary aspergillosis
5. Pulmonary eosinophillia associated with systemic disease
• EGPA
• HES
Aetiology
1. Primary (idiopathic)
2. Secondary
a) Known cause
• Drugs
• Toxins or irradiation
• Infections: parasitic, fungal and mycobacterial
b) Diseases associated with a degree of pulmonary eosinophilia
• Diffuse lung disease: idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, cryptogenic organising pneumonia, sarcoidosis and pulmonary Langerhans cell histiocytosis
• Malignancies: leukaemia, lymphoma, lung cancer, metastatic adenocarcinoma and metastatic squamous cell carcinoma
• Auto-immune diseases: rheumatoid arthritis, Sjögren's syndrome

Chronic eosinophilic pneumonia

The clinical disease entity CEP may be due to drugs, parasitic infections, irradiation or severe stressors such as childbirth.[10] Typically, however, it is idiopathic.

Carrington and colleagues first described a series of patients with this disease entity in 1969.[11] Idiopathic CEP (ICEP) is a rare disorder of unknown aetiology and there are no clear diagnostic criteria available. Table 3 suggests a schema.[12]

The exact prevalence of CEP remains unknown, but the disease is reported to contribute to <2.5% cases included in interstitial lung disease registries.[13] The peak incidence occurs in the fifth decade of life and females are twice as likely to be affected.[5] The overwhelming majority of patients are non-smokers, leading to the hypothesis that smoking may be protective. Presenting complaints commonly include cough, fever, dyspneoa and weight loss.[14] Wheezing, night sweats, malaise and a productive cough are less common, and haemoptysis is rare. Asthma is present in 50% of cases, and has usually been present for <5 years. Respiratory failure is less common than in AEP but has been reported in cases where the diagnosis was delayed.[15] Extrathoracic manifestations are ordinarily absent in CEP; when present, a diagnosis of EGPA or HES should be considered. Notably, a few patients with a diagnosis of CEP may develop minor extrathoracic manifestations without fulfilling diagnostic criteria for EGPA or HES. In addition, several authors have suggested that CEP may be a presenting feature of EGPA, suggesting a disease continuum.[16]

The most distinctive radiographic feature is the so-called 'photographic negative' of acute pulmonary oedema (Fig. 1). This is characterised by peripheral pulmonary infiltrates (consolidation or ground-glass opacification) which are usually bilateral but may occasionally be unilateral and migratory. Unfortunately this pattern is present in only 25% of cases, and in addition, has been described in cryptogenic organising pneumonia (COP), sarcoidosis or drug-induced pneumonia. Less frequent abnormalities include nodules, atelectasis and cavities.[14] Typically, interstitial fibrosis is minimal but there are reports of cases with progression to honeycombing.[17] Pleural effusions are rare, but a case of CEP presenting as bilateral massive pleural effusions has been reported.[18]

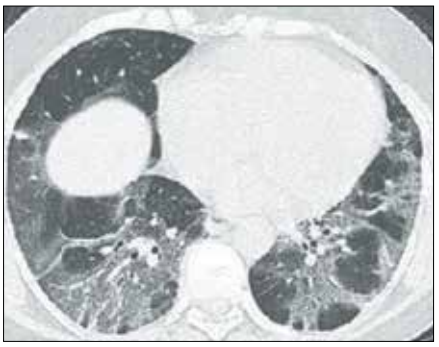

Fig. 1. Computed tomography (CT) scan showing CEP. Note the peripheral distribution of ground-glass opacities and the interlobular septal thickening. (Taken from www.chestatlas.com, with permission from Dr Harry Shulman.)

Peripheral eosinophilia, usually in excess of 1 000 cells/mm^3 is found in the majority of cases. There are anecdotal reports of cases of CEP without peripheral eosinophilia. In these cases the diagnosis is made on BAL, by the demonstration of >40% eosinophils in the fluid. In CEP, BAL always reveals an

abnormally high level of eosinophils. In contrast, transbronchial biopsy, when performed, may not reveal a significant eosinophilic infiltrate.[5] For this reason, in the rare instances where lung biopsy is required, the open modality is preferred. In keeping with the high proportion of atopic patients who develop CEP, immunoglobulin E (IgE) levels are elevated in 50% of cases.[10,12]

Pulmonary function tests may be normal in mild cases but usually show restrictive abnormalities with a reduced diffusing capacity. In patients with pre-existing asthma, obstructive defects may be noted. This is not due to CEP per se. Obstructive disease of the small airways may reflect a degree of bronchiolitis.[14] All patients with CEP will be hypoxaemic or demonstrate an increased A-a gradient.[5]

Clinical response to corticosteroids provides support for the diagnosis. The response is typically rapid: blood eosinophilia regresses within hours and radiographic abnormalities within days. Symptoms improve within weeks. There is no consensus with respect to dose or optimal duration of therapy but most authors recommend prednisone as the drug of choice. A dose of between 0.5 mg and 1 mg/kg/day is used initially and gradually tapered over a period of 6 months. Relapses are common and are said to occur in between 30 and 50% of cases.[10] Relapses may occur in the same or different parts of the lung[2] and respond as well to corticosteroids as the initial episode. There is a suggestion that 3 months of therapy may be as effective as 6 months, with no difference in relapse rate.[19] The use of inhaled corticosteroids has been suggested as a modality to reduce relapse rates and oral corticosteroid use. Marchand *et al.*[20] reported a reduced relapse rate in patients with CEP and asthma.More than half of patients with CEP require long-term systemic corticosteroid therapy due to frequent relapses or severe asthma. The side-effects of such therapy are well documented and, therefore, steroid-sparing strategies require consideration. Kaya *et al.*[21] reported the successful treatment of a single case of a patient with CEP and high IgE levels with omalizumab (a monoclonal antibody directed at IgE). This modality requires further study.

Table 2. Infectious causes of pulmonary eosinophilia*

Disease manifestation	Cause
Löffler's	*Acaris*
	Hookworm
	Schistosomiasis
Large parasite burden	Strongyloidiasis
Direct pulmonary penetration	Paragonimiasis
	Visceral larval migrans
Immunologic response to organisms (tropical filarial pulmonary eosinophilia)	Filariasis
	Dirofilariasis
Cystic disease (rare)	*Echinococcus*
	Cysticercosis
Fungal aetiologies	Coccidiomycosis
	Cryptococcosis
	Paracoccidiomycosis
	Basidiobolomycosis

*Adapted from Akuthota P, Weller PF.[7]

Table 3. Suggested diagnostic schema for ICEP

- Subacute or chronic respiratory and general symptoms (average of 7.7 months before diagnosis)
- Alveolar eosinophilia (>40% eosinophils at BAL) or peripheral eosinophilia (blood eosinophilia count >1 000 cells/mm^3
- Pulmonary infiltrates on chest imaging (usually peripheral predominance)
- Exclusion of known causes of eosinophilic lung diseases

Acute eosinophilic pneumonia

AEP, first described in 1989,[22] is differentiated from CEP by the duration and severity of symptoms and the absence of relapse after recovery. The diagnostic criteria proposed by Allen *et al.*[5] in 1994 are the most widely accepted criteria (Table 4). Some authors, however, have challenged the disease duration criterion[23] and have included patients with symptoms of up to 1 month's duration in case series.

Typically, patients are previously well and present with an acute febrile illness and hypoxaemic respiratory failure, sometimes meeting criteria for acute respiratory distress syndrome. Blood eosinophilia is typically absent; frank alveolar eosinophilia (usually >25% of cells) at BAL is the norm and can obviate the need for lung biopsy.[2] The mean age of patients at diagnosis is 30 years. There is a male predominance and typically no prior history of atopy. Idiopathic AEP (IAEP) is a diagnosis of exclusion and, to that end, very close attention should be paid to respiratory exposures within the days prior to presentation. Several exposures are purported to lead to the intense pulmonary eosinophilic infiltrate noted in AEP. Examples reported in the literature include cave exploration, plant repotting, indoor renovations, tank cleaning and exposure to various dusts including dusts at the World Trade Centre.[23,24] There have been several case reports of the development of AEP after the initiation of cigarette smoking,[2,25] but given that cigarette smoking is common and AEP is rare, smoking is unlikely the sole cause of AEP. Drugs, parasites and fungi are also known causes of this syndrome.

The precise mechanism of disease in IAEP has yet to be elucidated. An acute hypersensitivity reaction to an unidentified inhaled antigen has been put forward as a cause. The degree of respiratory failure in AEP is related to both the intensity of eosinophilic infiltration of pulmonary parenchyma and the mediators released by the eosinophils. In addition to cationic granule proteins and inflammatory lipid mediators, vascular endothelial growth factor is elevated in the lungs of patients with AEP, where it causes increased vascular permeability and alveolar filling.[26] The proteolytic potential of eosinophils is lower than that of neutrophils and this allows complete resolution.

The initial radiographic finding is a subtle interstitial infiltrate which progresses to a diffuse mixed interstitial and alveolar infiltrate within hours to days. Small to moderate-sized pleural effusions are common. In contrast to CEP, peripherally-based infiltrates are uncommon. The combination of diffuse areas of ground-glass attenuation, defined nodules, smooth interlobular septal thickening and pleural effusions may correctly identify the diagnosis in up to 81% of cases.[27]

Pulmonary function tests show a restrictive defect with a low diffusing capacity in the acute phase; these return to normal following treatment.

The key diagnostic differential is the exclusion of an infectious cause. Fungal pneumonia should always be excluded by fungal culture, as it can mimic the presentation of AEP.

A rapid response to corticosteroids is a clinical hallmark, but several cases of spontaneous resolution have been reported. High doses are required, but the minimum effective dose is not known. A regimen of intravenous methylprednisolone until respiratory failure has resolved, followed by oral prednisone for another 2 weeks has been used successfully.[5,23] Steroids are then tapered for the next 2 - 4 weeks. Importantly, several cases of spontaneous resolution have been reported.[28] Failure to respond to corticosteroid therapy should prompt a thorough search for an alternate diagnosis, particularly fungal infection.

AEP may be rapidly progressive, with patients occasionally requiring mechanical ventilation within hours. Fatalities have been reported in severe cases. AEP is easily diagnosed and treated and should be considered in all cases of unexplained respiratory failure and pulmonary infiltrates.

Allergic bronchopulmonary aspergillosis

The entity of ABPA refers to a complex hypersensitivity reaction to colonisation of the airways with *Aspergillus* spp. Exact prevalence is unknown. A vicious cycle with repeated episodes of bronchial obstruction, inflammation and mucoid impaction is set up. This can lead to bronchiectasis, fibrosis and eventual respiratory compromise.[29] Although most commonly seen with *Aspergillus fumigatus*, allergic bronchopulmonary disease has been described in association with *Candida albicans*, *Aspergillus terreus* and other fungal diseases.

ABPA occurs primarily in asthmatics (2 - 32%) and patients with cystic fibrosis (1 - 15%).[30] Both genders and any age group may be affected. The disease cycle mentioned above is the dominant presenting clinical feature. In addition to this, peripheral eosinophilia is present and haemoptysis may occur. Wheezing is often absent and an incidental finding of pulmonary consolidation may be the presenting feature. Chest X-rays (CXR) and CT scans may classically show bronchiectasis, patchy infiltrates and evidence of mucous impaction. Central bronchiectasis is associated with ABPA and is present in 85% of patients at diagnosis.[31] Those without central bronchiectasis should not be excluded, since it may be absent early in the disease course. Pulmonary function testing usually shows an obstructive defect.

The pathophysiology is not understood completely. Healthy individuals display low levels of IgG and IgA against fungal antigens, suggesting that they are able to eliminate fungal spores, even when inhaled in sufficient quantities to behave as an allergen. This is in contrast to atopic individuals who respond to inhalation of fungal spores by forming IgG and IgE. In addition, a Th2 response is elicited in affected individuals, leading to an increase in IL-4, IL-5 and IL-13, explaining the eosinophilia and raised IgE levels. The characteristic central bronchiectasis of ABPA is likely multifactorial in nature, with proteolytic enzymes, *Aspergillus* mycotoxins and neutrophilic and eosinophilic inflammation contributing.

The diagnosis of ABPA (at least in the USA) is based on the Patterson criteria.[31] Diagnosis is made using a combination of clinical, radiographic, serologic and immunologic findings. Four of the major clinical features listed in Table 5 are required for diagnosis. Importantly, these criteria are not universally applied, making overall prevalence difficult to study.

Pathology is not required for diagnosis but findings may include eosinophilic inflammation, mucoid impaction and bronchocentric granulomatosis. In addition, non-invasive, septated hyphae may be visible.

ABPA is said to progress through five clinical stages, as described by Patterson: acute, remission, exacerbation, corticosteroid-dependent asthma and fibrosis.[32] Treatment varies according to stage. Acute or recurrent flares are treated with systemic glucocorticoids; these are tapered over 3 - 6 months.[33] Antifungal agents effective against *Aspergillus* spp are used as adjunctive therapy to reduce the antigenic stimulus. Itraconazole is considered first-line therapy but voriconazole has also been used. Omalizumab has been reported as being effective in ABPA for reduction of exacerbations.[34]

Eosinophilic lung disease associated with systemic conditions

Eosinophilic granulomatosis with polyangiitis

This eponymous syndrome was first described in autopsied cases in 1951[35] and is a small vessel vasculitis.[36] Multiple organs may potentially be affected, including the sinuses, heart, lungs, gastrointestinal tract, skin and kidneys. The initial description was revised in 1990, when the American College of Rheumatology (ACR) established criteria for diagnosis (Table 6).[1]

At least four are necessary to confirm the diagnosis. Notably, this means that the histopathological criterion is not necessary for the diagnosis and clinical diagnosis is possible.[1] Lung biopsy is still considered the gold standard. However, nerve, muscle and skin biopsies may reveal perivascular eosinophilic infiltration and confirm the diagnosis. Renal biopsy tends to be nonspecific and therefore not useful. Despite the name EGPA, granulomata are not required for diagnosis. Antineutrophil cytoplasmic antibody (ANCA), particularly perinuclear ANCA, is positive in 50 - 70% of cases.[37]

Table 4. Diagnostic criteria for AEP

- Acute febrile illness <5 days' duration
- Hypoxaemic respiratory failure
- Diffuse alveolar or mixed alveolar-interstitial infiltrates on CXR
- >25% eosinophils on BAL
- Absence of parasitic, fungal or other infection
- Prompt and complete response to corticosteroids
- Failure to relapse after discontinuation of steroids

Table 5. Diagnostic criteria for ABPA

- Asthma
- Peripheral blood eosinophilia
- Immediate skin prick test for *Aspergillus* antigens
- Serum precipitating antibodies against *Aspergillus* antigens
- Increased serum IgE levels
- CXR infiltrates

Table 6. ACR diagnostic criteria for EGPA

- Asthma
- Eosinophil in peripheral blood >1 500 cells/mm^3 of blood
- Paranasal involvement
- Transient pulmonary infiltrates
- Mononeuropathy or polyneuropathy
- Biopsy findings of vasculitis

The clinical features of EGPA are well defined. The disease occurs most commonly in the fourth and fifth decades, both genders being affected. The syndrome is characterised by three phases:[38]

- Allergic phase: Asthma is always present and usually severe; rhinitis occurs in 75% of cases and is often accompanied by recurrent sinusitis and polyps.
- Eosinophilic phase: Severe persistent eosinophilia (more than 1 500 cells/mm^3) for at least 6 months.
- Vasculitic phase: Systemic manifestations and small-vessel vasculitis involving two or more extrapulmonary organs.

These phases may be dissociated.[1] Asthma precedes vasculitis by an average of 3 - 9 years,[38] but the interval may be longer or the two entities may coincide. The advent of vasculitis may be associated with a reduction is asthma severity.[1] Blood eosinophilia commonly parallels vasculitic activity and BAL fluid may contain in excess of 60% eosinophils. IgE levels are markedly increased and correlate with disease activity.[38] Ill-defined migratory pulmonary infiltrates are present in 37 - 72% of cases; the CXR may remain normal. High-resolution chest CT demonstrates nonspecific features that allow a correct diagnosis in fewer than half of cases.[27] Features include ground-glass attenuation, airspace consolidation, centrilobular nodules, bronchial wall thickening or bronchial dilatation, interlobular septal thickening, hilar or mediastinal lymphadenopathy, and pleural and pericardial effusions. Pulmonary cavitatory lesions are rare.

Multi-organ involvement is possible. Upper airway manifestations have been alluded to. Skin manifestations are present in 70% of cases and can include nodules, palpable purpura or urticaria. Nervous system involvement includes mononeuritis multiplex in 66% of cases. Gastrointestinal symptoms may include abdominal pain, diarrhoea and bleeding. Cardiac findings include cardiac failure, pericarditis, endomyocardial fibrosis, valvulitis, coronary vasculitis and systemic hypertension. Cardiac manifestations are a poor prognostic feature and contribute to 50% of deaths. Many patients have fever, myalgias or arthralgias and lymphadenopathy.[38] Uncommon manifestations include hearing loss, reversible exophthalmos and pulmonary capillaritis.[39]

Corticosteroids alter the natural history of this disease. Fifty per cent of untreated patients die within 3 months of the onset of vasculitis. This increases dramatically to a mean of 9 years in those undergoing corticosteroid treatment.[40] Several weeks of prednisone in high doses are required to halt the vasculitis and mononeuritis may require more prolonged treatment. Daily or alternate-day doses of prednisone are typically continued for a year and then weaned. Relapses after this are uncommon.[39] Treatment of asthma with inhaled corticosteroids may allow reduction in the dose of systemic steroids. Alternative treatment options for non-responders include high-dose pulses of methylprednisolone, azathioprine or cyclophosphamide.[41,42] In some patients, the treatment of the severe asthma associated with EGPA with systemic steroids may mask the vasculitis and discontinuation of steroids or reduction in the dose may unmask it. Cases of 'limited' EGPA, the so-called 'formes frustres' have been reported. These refer to forms with single organ involvement and may resemble other eosinophilic syndromes such as ICEP.[43]

There have been several reports of EGPA associated with leukotriene inhibitors, but a causative role has yet to be conclusively established.[44] Some authors suggest that these agents should be avoided in asthmatics with marked eosinophilia or features compatible with EGPA.[2]

The hypereosinophilic syndrome

The hypereosinophilic syndromes are a group of diseases defined by sustained eosinophil overproduction in association with tissue infiltration or damage. The term HES is reserved for those cases fulfilling the above definition, in which all known potential causes have been excluded (parasites, drugs or non-haematological neoplasia). Blood hypereosinophilia is defined as an absolute eosinophil count of greater than 1.5×10^9/L on two examinations, at least one month apart. Tissue infiltration is defined as:

- >20% eosinophils on bone marrow biopsy and/or
- extensive tissue infiltration of eosinophils (in the pathologist's opinion) and/or
- marked deposition of eosinophil granule proteins in the absence of marked eosinophilic infiltration.[45]

HES may be defined as primary, secondary or idiopathic. Primary (neoplastic) HES is the result of eosinophilic expansion that is clonal, such as in underlying stem cell, myeloid or eosinophilic neoplasia. Secondary (reactive) HES is the result of polyclonal stimulation of eosinophil cytokines. Long-term follow-up of patients with 'idiopathic' HES often reveals a clonal process. The HES has been further sub-categorized into several variants (Table 7). These variants are distinct entities with clinically important differences in diagnosis, therapeutics and prognosis.

Table 7. HES variants

Myeloproliferative variants
T-cell lymphocytic variants (L-HES)
Familial HES
Idiopathic HES
Organ-restricted HES
Specific or defined syndromes associated with hypereosinophilia
episodic angioedema with eosinophilia

In the lymphocytic variant, it is postulated that an abnormal clonal proliferation of Th2 helper cells is responsible for the profound eosinophilia.[46] The myeloproliferative type is so termed because it shares features common to other myeloproliferative diseases,

including hepatosplenomegaly, cytopenias, elevated serum vitamin B_{12} and presence of immature forms in peripheral blood.

Males are seven to nine times more likely to be affected than females. Usual age of onset is in the third of fourth decade. Constitutional symptoms such as anorexia, night sweats and fever dominate the presentation. Cardiac involvement portends a poor prognosis; endomyocardial fibrosis is the main cardiac manifestation and is more commonly seen in the myeloproliferative variant.[47] In a retrospective review of 50 patients with HES,[48] 40% of patients suffered pulmonary involvement, 62% of patients in the study suffered neurological involvement including thrombotic cerebrovascular accidents, cognitive decline, movement disorders and peripheral neuropathy and 56% of patients had skin manifestations (angioedema, dermatographism and urticaria).

Organ cytotoxicity is largely caused by eosinophilic cationic granules such as MBP. In addition, cationic proteins induce a hypercoagulable state resulting in endothelial dysfunction with microangiopathies and cardiac mural thrombi. Long-standing HES may result in pulmonary fibrosis.

HES should be considered in patients with persistent blood hypereosinophilia on two occasions at least a month apart, regardless of whether symptoms are present or not. Once all known causes have been ruled out, a search for end-organ damage should be undertaken. Functional and anatomical assessments of the cardiovascular, pulmonary and gastrointestinal system should be undertaken and tissue samples obtained where appropriate. Bone marrow aspiration and trephine (BMAT) will always show increased mature eosinophils and precursor forms. It may help to identify a clinically important subtype or previously unknown cause. Routinely performed tests on BMAT include karyotyping, *in situ* hybridisation techniques for known mutations such as the Fip1-like1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFRA)-associated mutation, CD34 expression and molecular testing for the JAK 2 mutation.[49]

Corticosteroids are effective first-line therapy in less than half of patients,[5] necessitating the use of other treatment modalities including chemotherapeutic agents, cyclosporine and interferon-α.[47,50,51] Imatinib, a tyrosine kinase inhibitor, is effective in patients with the myeloproliferative form of HES who are refractory to steroids, hydroxyurea or interferon-α. Mepolizumab, an anti-IL-5 monoclonal antibody, may be effective as well.[52] Due to better diagnostics and therapeutic options, 10-year survival rates may be as high as 70%.[50]

Conclusions

Clearly, eosinophilic lung diseases are a heterogeneous group of disorders that are not easily classifiable. Peripheral eosinophilia is a diagnostic clue. In its absence, the diagnosis is often not considered until eosinophilia is noted on BAL fluid or a lung biopsy specimen or radiological appearance is thought to be suggestive. History and examination provide vital diagnostic information and a thorough inquiry into prescription, non-prescription and illicit drug use and other possible exposures is vital. Information regarding the severity and duration of symptoms can help to narrow the differential. A history of asthma may be found in EGPA, CEP and ABPA. Travel to tropical areas (recent or remote) raises the possibility of parasitic infections. Ancillary investigations can be of use, especially in ABPA and pulmonary eosinophilia associated with systemic disease. Symptoms of an underlying auto-immune disease or malignancy should be specifically sought.

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