Eosinophilic Pneumonia

17

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Introduction

The eosinophilic lung diseases (Table 17.1) are characterized by the presence and presumed pathogenetic role of eosinophils in the lesional processes. Eosinophilic pneumonias are defined by a prominent infiltration of the lung parenchyma by eosinophils. The other eosinophilic lung diseases, mainly hypereosinophilic asthma (not discussed in this chapter), allergic bronchopulmonary aspergillosis, and the recently individualized hypereosinophilic obliterative bronchiolitis, mainly involve the airways.

Table 17.1 Definition of eosinophilia and hypereosinophilia

Term	Definition
Blood eosinophilia	>0.5 eosinophils × 10^9/L blood
Hypereosinophilia	>1.5 eosinophils × 10^9/L blood
Alveolar eosinophilia	>25% eosinophils at bronchoalveolar lavage
Tissue hypereosinophilia	• Percentage of eosinophils in bone marrow section exceeds 20% of all nucleated cells and/or
	• Pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or
	• Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils)

Eosinophil Biology

Initially thought to be especially important in the defense against parasitic infestation, eosinophil leukocytes are now considered multifunctional cells implicated in the initial stage of innate and adaptive immunity, including but not restricted to numerous inflammatory reactions to parasitic helminth, bacterial, and viral infections [1]. Their broad role in homeostatic function, physiology, and pathophysiology is now well appreciated [2].

Eosinophil Differentiation and Recruitment

Eosinophil precursors differentiate and mature in the bone marrow under the action of cytokines and especially interleukin (IL)-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [1, 3]. Activation of the Ddbl-GATA-1 transcription factor is deemed critical in this process. Mature eosinophils then circulate in the blood for about 1 day before being attracted into tissues, through processes of chemotaxis, adhesion, and diapedesis that are primarily under the control of IL5 and eotaxin-1, itself regulated by the Th2 cell-derived IL-13 cytokine. In the tissues, they undergo apoptosis unless survival factors (mostly IL-5) are present.

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Physiologic and Immunologic Role of Eosinophils

Physiologic roles of eosinophils include their participation in host defense response, tissue regeneration, tissue repair after injury, metabolic homeostasis, immune homeostasis, angiogenesis, fibrosis, steady-state development of intestine and mammary gland, and tumor rejection [2, 4]. The eosinophil is involved in many allergic or inflammatory processes through its interaction not only with other cells, including especially T helper (Th) lymphocytes, but also with mast cells and basophils, endothelial cells, macrophages, platelets, and fibroblasts [2, 3]. Intercellular signaling is mediated by surface expression of adhesion molecules, apoptotic signaling molecules, chemokines, complement receptors, chemotactic factor receptors, cytokine receptors, and immunoglobulin receptors. For instance, eosinophils are capable of regulating mast cell function and histamine release. Eosinophils have further immune properties. They express the major histocompatibility complex II protein human leukocyte antigen (HLA)–DR, can present the antigen to T-helper lymphocytes, and secrete an array of cytokines, thereby promoting effector T-cell proliferation. They can synthesize IL-4 and promote IL-4, IL-5, and IL-13 secretion by $CD4^+$ T-cells (promoting Th2 lymphocyte activation), and secrete indoleamine 2,3-dioxygenase (indirectly promoting Th1 apoptosis), modulating the Th1/Th2 balance. Abnormalities in the T-cell receptor repertoire and T-cell clonotype of BAL lymphocytes and peripheral blood lymphocytes seem to contribute to the pathophysiology of eosinophilic lung diseases [5]. Overall, the paradigm of eosinophil function has changed from a terminal effector cell in allergic airway diseases to its being involved in the initial stages of pathophysiology.

Release of Mediators

The eosinophil contains two types of intracytoplasmic granules, the content of which can be released by exocytosis, piecemeal degranulation, or cytolysis, while other mediators are secreted (with the involvement of vesicle-associated membrane proteins in the regulation of granule fusion within the cell). Granule release through cytolysis is a rapid, stimulus-dependent process, and specific in terms of which cytokines are secreted.

The larger granules, identified by a dense crystalloid matrix at electron microscopy, contain the characteristic cationic proteins major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and the enzymatic protein eosinophil peroxidase (EPO) [1, 3, 4]. The smaller amorphous granules contain arylsulfatase and acid phosphatase. The process of degranulation by activated eosinophil releases cationic proteins into the extracellular space, with potential direct toxicity to the heart, brain, and bronchial epithelium. Degranulated eosinophils can be identified with electron microscopy by the presence of cytoplasmic vacuoles, and loss of electron density of the central core of the granules (inversion or disappearance of core density). Molecular and intracellular pathways regulating eosinophil differentiation, priming, activation, degranulation, and mediator secretion, and how the release of toxic substances contributes to the pathophysiology of eosinophilic disorders, have become better understood from a molecular standpoint [3].

In addition to cationic proteins, eosinophils release a number of preformed mediators including proinflammatory cytokines, lipid- and arachidonic acid-derived mediators, enzymes, reactive oxygen species, and matrix metalloproteases [4], all of which may contribute to the pathophysiology of eosinophilic lung diseases. Histopathologic lesions in eosinophilic pneumonias are formed by the recruitment of activated eosinophils and other inflammatory cells to tissues, and are largely reversible with treatment, especially with corticosteroids. However, tissue damage and remodeling with fibrosis may occur partly through the release by eosinophils of transforming growth factor-beta, especially in the bronchial mucosa, as in allergic bronchopulmonary aspergillosis (ABPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg–Strauss syndrome).

Targeting the Eosinophil Cell Lineage

Corticosteroids shorten eosinophil survival in the blood and tissues and are among the most potent drugs to treat eosinophilic disorders, although lack of specificity can result in numerous adverse events. As the recruitment of eosinophils to the lung mostly implicates IL-5 and the eotaxin subfamily of chemokines (itself regulated by the Th2 cell-derived IL-13 cytokine), the IL-5 pathway is the target of several drugs, initially developed in asthma, and which have dramatically changed the therapeutic landscape of various eosinophilic disorders. Several other biologic therapies are already licensed to suppress type 2 inflammation via IgE and IL-4 receptor alpha [6]. Other targets for therapy more specific for eosinophils are being investigated including eotaxins, which drive eosinophil recruitment into tissues, CD2-binding protein, and eosinophil surface-expressed inhibitory receptors especially Siglec-8 [2, 4, 7] (Table 17.2).

Table 17.2 Main drugs targeting the eosinophil lineage

Drug	Target
Omalizumab	Immunoglobulin E
Mepolizumab	Interleukin-5
Reslizumab	Interleukin-5
Benralizumab	Interleukin-5 receptor-α
Dupilumab	Interleukin-4 receptor-α
Lebrikizumab	Interleukin-13
RPC4046	Interleukin-13
AK002	Siglec-8

General Features of Eosinophilic Pneumonias

Historical Perspective

Early descriptions of pulmonary "infiltration with eosinophilia" [8], "pulmonary eosinophilia" [9], and later of "cryptogenic pulmonary eosinophilias" [10] included cases now considered as probable idiopathic chronic eosinophilic pneumonia (ICEP), EGPA, and Löffler syndrome. Carrington and colleagues [11] described in 1969 the syndrome of ICEP.

Clinical Presentation

Eosinophilic pneumonia is pneumonia where the eosinophils are the most prominent inflammatory cells on histopathologic examination, whereas infiltration with lymphocytes and neutrophils does not predominate. Eosinophilic pneumonias are separated into two main etiologic categories: (1) those with a definite cause and (2) idiopathic eosinophilic pneumonias, either solitary or associated with extrathoracic manifestations that are a hallmark of EGPA, but can also be observed, to a lesser extent, in hypereosinophilic syndromes (HES), drug reactions, or infections, especially parasitic infections. It is therefore mandatory that the clinician take a full history and search thoroughly for a cause with potentially practical consequences, such as parasitic infection or drug or toxic exposures.

Most eosinophilic pneumonias can be classified within one of the well-characterized and individualized syndromes. They may manifest in different clinicoradiologic syndromes, namely Löffler syndrome, chronic eosinophilic pneumonia, or acute eosinophilic pneumonia, mostly differing from one another by the pattern of disease onset, severity, and evolution with or without corticosteroid treatment. The recent description of eosinophilic vasculitis, with systemic manifestations [12] or limited to the lung [13], has further drawn attention to vascular involvement that rarely may be present in eosinophilic pneumonias. The vast majority of cases of eosinophilic pneumonia respond dramatically to corticosteroid treatment [14] and heal without significant sequelae.

Pathology

Open lung biopsies that used to be performed for the diagnosis of ICEP have provided material for the few histopathologic studies published on eosinophilic pneumonia [10, 11, 15]. The pathologic features described in ICEP represent a common denominator of all categories of eosinophilic pneumonias, whatever their origin. Additional specific features may be observed depending on the etiological context (e.g., bronchocentric distribution of lesions in ABPA; the presence of parasites or fungal hyphae in eosinophilic pneumonia of parasitic origin; granulomas and eosinophilic vasculitis in EGPA; prominent eosinophilic vasculitis in idiopathic eosinophilic vasculitis).

In ICEP, the alveolar spaces are filled with eosinophils representing the predominant inflammatory cell, together with a proteinaceous and fibrinous exudate, respecting the global architecture of the lung. The distribution of eosinophilic pneumonia is generally diffuse. Macrophages are also present in the infiltrate, with scattered multinucleated giant cells occasionally containing eosinophilic granules or Charcot-Leyden crystals [11]. An associated interstitial inflammatory cellular infiltrate is invariably present, consisting of eosinophils, lymphocytes, plasma cells, and histiocytes. Some eosinophilic microabscesses may be observed (foci of necrotic intra-alveolar eosinophils surrounded by macrophages or epithelioid cells with a palisading arrangement). Degranulated eosinophils can be identified within the site of eosinophilic pneumonia by electron microscopic or immunohistochemical studies [16]. Areas of non-prominent organization of the alveolar inflammatory exudate are common [11]. Mucus plugs obstructing the small airways may be present in ICEP [11] and especially in ABPA. A mild *non-necrotizing* vasculitis involving both small arteries and venules is common; however, necrosis and fibrosis are absent.

In idiopathic acute eosinophilic pneumonia (IAEP), the pathologic pattern includes intra-alveolar and interstitial eosinophilic infiltrates, diffuse alveolar damage, and intra-alveolar fibrinous exudates, organizing pneumonia, and non-necrotizing vasculitis [17].

Diagnosis

The clinical diagnosis of eosinophilic pneumonia is suspected in patients with respiratory symptoms (dyspnea, cough, or wheezing), pulmonary opacities at chest imaging, and eosinophilia demonstrated in the peripheral blood and/or in the lung.

Bronchoalveolar lavage (BAL) is a good surrogate of lung biopsy to demonstrate lung eosinophilia, although no study has definitely established a correlation between increased eosinophils at differential cell count and eosinophilic pneu-

monia at lung pathology. In normal subjects, BAL eosinophilia is lower than 1% of cells at the differential count. In contrast, BAL eosinophilia greater than 40% is found mainly in patients with chronic eosinophilic pneumonia, whereas BAL eosinophilia between 3% and 40% (and especially between 3% and 9%) may be found in various interstitial lung diseases other than eosinophilic pneumonia. A conservative cutoff of 40% of eosinophils at BAL differential cell count has been adopted for the diagnosis of ICEP in clinical studies [18, 19], and a cutoff of 25% has been proposed for the diagnosis of IAEP [20]. We recommend that a clinical diagnosis of eosinophilic pneumonia be supported by alveolar eosinophilia when the eosinophils (1) are the predominant cell population of BAL cell count (macrophages excepted) and (2) represent more than 25% of differential cell count (acknowledging that the specificity is higher when the eosinophil cell count is greater than 40%). BAL is recommended to confirm the diagnosis of eosinophilic pneumonia in most cases.

Blood eosinophilia when present also contributes to the diagnosis of eosinophilic pneumonia in a patient with compatible HRCT features. It may be missing in patients who have already received systemic corticosteroids, and it is often absent at presentation in IAEP. Blood cell count must therefore be measured before starting corticosteroids. In normal subjects, however, blood eosinophil count is a continuous, rather than dichotomous, variable, and may be influenced by a variety of factors such as age, sex, atopy, and environmental exposure. Median eosinophil counts are typically between 100 and 160 cells/μL [21]. In the setting of eosinophilic lung diseases, *blood eosinophilia* has generally been defined by an eosinophil blood count greater than 0.5×10^9/L (500 cells/μL) (Table 17.3). It was further proposed to define *hypereosinophilia* as an eosinophil blood count greater than 1.5×10^9/L on two examinations over at least a 1-month interval, and/or tissue hypereosinophilia [22, 23]. Frank blood eosinophilia (e.g. greater than 1×10^9/L), and preferably hypereosinophilia, may obviate the need to perform BAL in the individual cases with typical presentation. For example, BAL may occasionally be omitted to confirm Löffler syndrome (as it occurs in ascariasis) in a patient with a mild cough, wheezes, transient pulmonary opacities at chest radiograph, and frank blood eosinophilia. However, BAL is generally useful to rule out alternative diagnoses (such as bacterial or parasitic pneumonia, or pulmonary infiltrates related to Hodgkin's disease), and is generally recommended.

Video-assisted thoracoscopic lung biopsy or transbronchial cryobiopsies are seldom necessary, especially if pulmonary eosinophilia has been demonstrated by BAL. Biopsies are therefore generally discouraged, and considered only in difficult cases where a differential diagnosis to eosinophilic pneumonia is contemplated (e.g. eosinophilic vasculitis, primary pulmonary lymphoma, etc.). Although they can show characteristic features of eosinophilic pneumonia, forceps transbronchial lung biopsies are generally not recommended either due to the small size of the specimens that allows only partial morphologic evaluation.

Table 17.3 Classification of the eosinophilic lung diseases

Eosinophilic lung disease of undetermined cause
Idiopathic eosinophilic pneumonias
Idiopathic chronic eosinophilic pneumonia
Idiopathic acute eosinophilic pneumonia
Eosinophilic granulomatosis with polyangiitis
Idiopathic systemic eosinophilic vasculitis
Hypereosinophilic syndrome
Idiopathic hypereosinophilic obliterative bronchiolitis
Eosinophilic lung disease of determined cause
Eosinophilic pneumonias of parasitic origin
Tropical eosinophilia
Ascaris pneumonia
Eosinophilic pneumonia in larva migrans syndrome
Strongyloides stercoralis infection
Eosinophilic pneumonias in other parasitic infections
Eosinophilic pneumonias of other infectious causes
Allergic bronchopulmonary aspergillosis and related syndromes
Allergic bronchopulmonary aspergillosis
Other allergic bronchopulmonary syndromes associated with fungi or yeasts
Bronchocentric granulomatosis
Drug, toxic agents, and radiation-induced eosinophilic pneumonias
Drugs (typical, occasional, or exceptional eosinophilic pneumonia)
Toxic agents (illicit drugs, vaping)
Eosinophilic pneumonia induced by radiation therapy to the breast
Miscellaneous lung diseases with possible associated eosinophilia
Organizing pneumonia
Asthma
Eosinophilic bronchitis
Idiopathic interstitial pneumonias
Pulmonary Langerhans cell histiocytosis
Malignancies
Other

Eosinophilic Lung Disease of Undetermined Cause

ICEP is characterized by a progressive onset of symptoms over a few weeks with cough, increasing dyspnea, malaise, and weight loss, whereas IAEP presents as acute pneumonia (similar to acute lung injury or acute respiratory distress syndrome [ARDS]) with frequent respiratory failure necessitating mechanical ventilation. Both conditions are idiopathic.

Idiopathic Chronic Eosinophilic Pneumonia

Chronic eosinophilic pneumonia was first described in detail by Carrington and colleagues [11], in a series of nine patients, and further confirmed and detailed by several and numerous case reports.

Clinical Features

ICEP predominates in women with a 2:1 female-to-male ratio [15, 19], with a peak of incidence in the fourth decade [15], and a mean age of 45 years at diagnosis [19]. A majority of patients with ICEP are nonsmokers [15, 19], suggesting that smoking might be protective. About half of the patients have a history of atopy [15, 19] and up to two-thirds have a history of asthma [15, 18, 19, 24, 25], with no particularities in the clinical presentation of ICEP with the exception of higher total immunoglobulin (Ig) E levels in asthmatics [18]. In addition, asthma may develop concomitantly with the diagnosis of ICEP (15% of patients) or develop after ICEP (about 15% of patients) [18]. Asthma in patients with ICEP often gets worse and requires long-term oral corticosteroid treatment [18].

ICEP is characterized by the progressive onset of cough, dyspnea, and chest pain [15, 19], with a mean interval between the onset of symptoms and the diagnosis of 4 months [19]. Mechanical ventilation may be required on exceptional occasions. Hemoptysis is rare but can occur in up to 10% of cases [15, 19]. Chronic rhinitis or sinusitis symptoms are present in about 20% of patients [19]. At lung auscultation, wheezes are found in one-third of patients [15] and crackle in 38% [19]. Systemic symptoms and signs are often prominent, with fever, weight loss (>10 kg in about 10%), and commonly asthenia, malaise, fatigue, anorexia, weakness, and night sweats.

Imaging

The imaging features of ICEP are characteristic, although they may overlap with those found in cryptogenic organizing pneumonia. Peripheral opacities at chest X-ray present in almost all cases [11, 15, 19, 26, 27] consist of alveolar opacities with ill-defined margins, with a density varying from ground-glass to consolidation (Fig. 17.1), and are migratory in 25% of patients [19]. The classic pattern of "photographic negative or reversal of the shadows usually seen in pulmonary edema," highly evocative of ICEP, is seen in only one-fourth of patients [15]; however, peripheral and upper zone predominance of abnormalities is usually present.

Whereas the opacities are bilateral in at least 50% of cases at chest X-ray [15], the proportion of bilateral opacities increases up to more than 95% at high-resolution computed tomography (HRCT) [19] (Fig. 17.2). Predominance of ground-glass attenuation and consolidation in the periphery and upper lobes of both lungs [15, 19] is very suggestive of

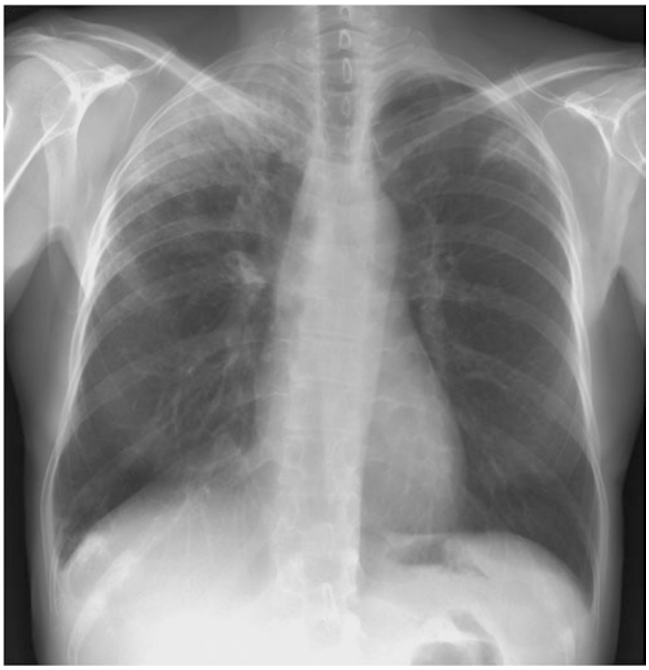

Fig. 17.1 Chest radiograph of a patient with idiopathic chronic eosinophilic pneumonia showing peripheral alveolar opacities predominating in the right upper lobe

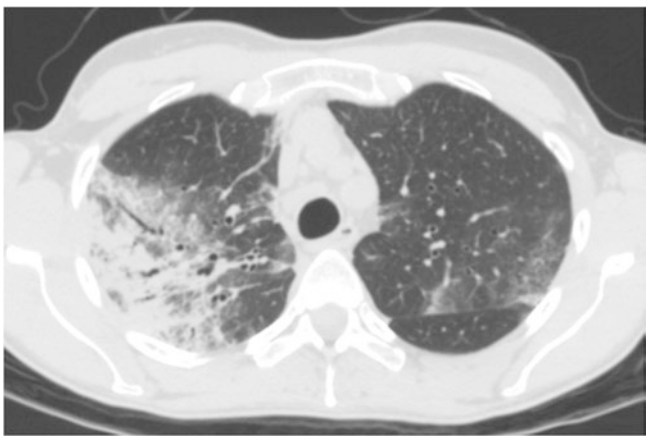

Fig. 17.2 Computed tomography (CT) scan of a patient with idiopathic chronic eosinophilic pneumonia showing bilateral asymmetric peripheral alveolar opacities with airspace consolidation and ground glass opacities

ICEP [19, 27, 28] (Fig. 17.3). Septal line thickening is common [28]. Centrilobular nodules (less than 20% of cases) [27], consolidation with segmental or lobar atelectasis, can also be seen. Upon corticosteroid treatment, consolidation rapidly decreases in extent and density, possibly evolving to ground-glass attenuation or inhomogeneous opacities, and later to streaky or bandlike opacities parallel to the chest wall. Cavitary lesions are extremely rare and should lead to reconsideration of the diagnosis. Reverse halo sign suggestive of organizing pneumonia is rare in ICEP. Pleural effu-

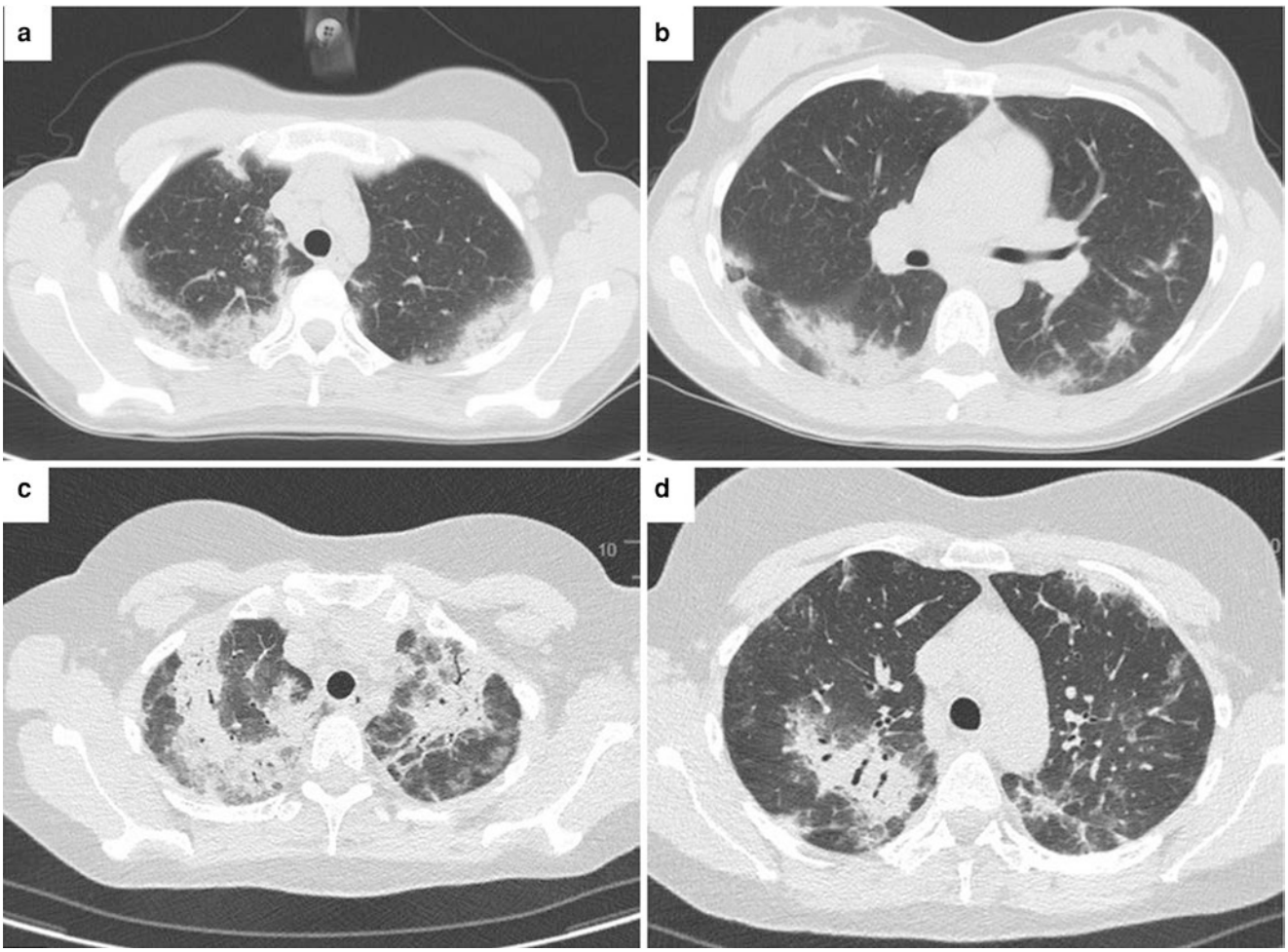

Fig. 17.3 Computed tomography (CT) scan of a patient with idiopathic chronic eosinophilic pneumonia at the time of diagnosis (**a**, **b**) and at the time of relapse 11 years later (**c**, **d**). Bilateral peripheral airspace consolidation predominates in the upper lobes

sions (which are common in IAEP) are rare and usually mild or moderate in ICEP. Mediastinal lymph node enlargement may be seen in 15–20% of cases [19].

Laboratory Studies

Peripheral blood eosinophilia is a diagnostic criterion of ICEP, and therefore the proportion of patients with ICEP and possible normal peripheral blood count is unknown. The mean blood eosinophilia was 5.5×10^9/L in the French series [19]. Eosinophils represent 26–32% of the total blood leukocyte count [15, 19]. C-reactive protein level is elevated [15, 19]. Total blood IgE level is increased in about half of the cases and greater than 1000 kU/L in 15% [19]. Antinuclear antibodies may occasionally be present [19]. Urinary EDN level indicating active eosinophil degranulation is markedly increased [29].

Bronchoalveolar Lavage

BAL eosinophilia is constant and key to the diagnosis of ICEP, obviating the need for lung biopsy (Table 17.4). The mean eosinophil percentage at BAL differential cell count was 58% at diagnosis in the French series [19]; however, the eosinophil count drops within a few days (or hours) upon corticosteroid treatment. The percentage of neutrophils, mast cells, and lymphocytes a BAL may be increased [19]. Sputum eosinophilia may also be present, although it is not a necessary tool for the diagnosis. Importantly, BAL contributes to rule out potential causes of eosinophilic pneumonia including infections, lymphoma, etc., and therefore must include both analyses of the differential cell count and microbiology.

Table 17.4 Diagnostic criteria for idiopathic chronic eosinophilic pneumonia

1.	Diffuse pulmonary alveolar consolidation with air bronchograms and/or ground glass opacities at chest imaging, especially with peripheral predominance
2.	Eosinophilia at BAL differential cell count ≥40% (or peripheral blood eosinophils $\geq 1.0 \times 10^9$/L)
3.	Respiratory symptoms present for at least 2–4 weeks
4.	Absence of other known causes of eosinophilic lung disease (especially exposure to a drug susceptible to induce pulmonary eosinophilia)

BAL eosinophils of patients with ICEP show features of cell activation and release eosinophil proteins, which are phagocytosed by macrophages. ECP and EDN levels are increased in the BAL fluid. Eosinophils are recruited to the lung through various chemokines and are resistant to Fas-induced apoptosis. Eosinophilic activation may be compartmentalized to the lung, as expressed by differential expression of HLA-DR molecules between alveolar and blood eosinophils. BAL lymphocytes include $CD4^+$ memory T-cells (expressing $CD45RO^+$, $CD45RA^-$, $CD62L^-$), and may present clonal rearrangement of the T-cell receptor repertoire [5].

Differential Diagnosis

Extrapulmonary manifestations when present challenge the diagnosis of ICEP and especially suggest the diagnosis of EGPA or overlap between ICEP and EGPA. Arthralgias, repolarization (ST-T) abnormalities on the electrocardiogram, pericarditis, altered liver biologic tests, eosinophilic lesions at liver biopsy, mononeuritis multiplex, diarrhea, skin nodules, immune complex vasculitis in the skin, and eosinophilic enteritis have been occasionally reported in ICEP [11, 19]; however, some cases would likely now be considered EGPA (e.g. eosinophilic pneumonia associated with mononeuritis multiplex). Furthermore, eosinophilic pneumonia may be a presenting feature of EGPA; corticosteroid treatment prescribed for ICEP may prevent the subsequent development of overt systemic vasculitis.

Lung Function Tests

An obstructive ventilatory defect is present in about half the patients [15, 19], and a restrictive ventilatory defect in the other half [19]. The carbon monoxide transfer factor (DLco) is decreased in half of the patients, and the transfer coefficient (DLco/unit alveolar volume, or Kco) is about one fourth. Hypoxemia ($PaO_2 < 75$ mmHg) present in two-thirds of patients [19] may be due to right-to-left shunting in consolidated areas of the lung, as suggested by increased alveolar-arterial oxygen gradient [15].

With treatment, the lung function tests rapidly return to normal in most patients [15]. However, a persistent ventilatory obstructive defect (not responsive to inhaled corticosteroids and bronchodilators) may develop over years in up to a third of patients, especially those with concurrent asthma and obstructive defects at diagnosis [30]. In one study, the persistence of a ventilatory obstructive defect was associated with a markedly increased BAL eosinophilia at initial evaluation [31].

Treatment

Because most patients receive corticosteroids, the natural course of untreated ICEP is not well known [15]. However, spontaneous resolution of ICEP may occur [15, 19]. The clinical and radiologic response to corticosteroids is dramatic, with the improvement of symptoms within 1 or 2 weeks and even within 48 h in about 80% [19] of cases, and rapid clearance of pulmonary opacities on chest X-ray. In one series, the chest radiograph was significantly improved at 1 week in 70% of patients, and almost all had a normal chest X-ray at their last follow-up visit [19]. Death directly resulting from ICEP is exceedingly rare.

The optimal dose of corticosteroids is not established, but treatment may be initiated with 0.5 mg/kg/day of prednisone, with slow tapering over 6–12 months based on clinical evaluation and blood eosinophil cell count. In an open-label, randomized study, no significant difference was found in the cumulative rate of relapse between patients with CEP randomized to receive oral prednisolone for either 3 or 6 months [32]. Treatment may therefore be initiated with 0.5 mg/kg/day of prednisone, with slow tapering down to 5–10 mg/day over 3 months based on clinical evaluation and blood eosinophil cell count.

Most patients require treatment for longer than 6–12 months because of relapse in more than half of patients while decreasing below a daily dose of 10–15 mg/day of prednisone, or after stopping oral corticosteroid treatment [15, 19]. Relapses respond very well to corticosteroid treatment, which usually can be resumed at a dose of about 20 mg/day of prednisone [19, 32].

Outcome and Perspectives

The clinical series in which long-term follow-up is available clearly show that most patients need very prolonged corticosteroid treatment: in a series with a mean follow-up of 6.2 years, only 31% were weaned at the last control visit [19]. In a series of 133 cases, relapse occurred in 56% of patients during a follow-up period of over 6 years [30]. Relapses of ICEP must be distinguished from asthma symptoms and may be less frequent in asthmatics, possibly because of inhaled corticosteroids prescribed after stopping oral corticosteroids [18, 19]. Alternate-day prescription of oral corticosteroids may reduce the adverse events of treatment. Inhaled corticosteroids might thus help in reducing the maintenance dose of oral corticosteroids, although they are not effective enough when given as monotherapy [33].

Long-term use of corticosteroids may lead to a variety of adverse events including osteoporosis and weight gain, which has to lead to consider steroid-sparing agents. Omalizumab, a recombinant humanized monoclonal antibody against IgE, was reported to prevent recurrence of ICEP and to spare oral corticosteroids in case reports; however, caution must be exerted given recent reports of omalizumab-associated EGPA [34, 35].

The anti-IL-5 monoclonal antibody mepolizumab and the IL-5-receptor antagonist benralizumab have been used in case reports of patients also suffering from severe eosinophilic asthma, but have not yet been evaluated properly in

patients with ICEP. Outside of the indication of severe eosinophilic asthma, and because of the exquisite sensitivity of ICEP to corticosteroids, the use of these agents should be restricted to exceptional cases of ICEP with frequent relapses of eosinophilic pneumonia preventing tapering of corticosteroids and/or intolerance or contraindications to oral corticosteroids. Cases considered refractory to corticosteroids should lead to reconsidering the diagnosis of ICEP.

Idiopathic and Smoking-Related Acute Eosinophilic Pneumonia

IAEP is often misdiagnosed as infectious pneumonia because of fever and bilateral opacities on chest X-ray present in all patients. However, IAEP [17, 20, 25, 36–41] markedly differs from ICEP by its acute onset, the severity of hypoxemia, the usual lack of increased blood eosinophils at presentation contrasting with highly increased eosinophil percentage at BAL, and the absence of relapse after clinical recovery. Because fever and bilateral opacities on chest radiograph are present in nearly all patients, IAEP is often misdiagnosed as infectious pneumonia [20]. Known causes of acute eosinophilic lung disease, particularly drug exposure, infection, or vaporized cannabis oil, must be excluded for the diagnosis of IAEP to be made (Table 17.5) [42, 43].

Clinical Features

IAEP may present at any age [44]; however, most patients are aged 20–40 years [20, 44, 45], with a very strong predominance in males [39]. Most patients have no prior asthma history [25]. However, taking a thorough exposure history is mandatory, as a causative role of cigarette smoke is established. Most patients have been recently exposed to dust or cigarette smoke within the days before the onset of disease, and often will have begun to smoke, restarted to smoke, or increased the number of cigarettes smoked daily, especially within 1 month before the onset of "idiopathic" AEP [39, 46]. The disease is therefore often not "idiopathic," being initiated or triggered by inhaled nonspecific causative agents in susceptible individuals; however, it can occur in the absence of any inhaled exogenous trigger. AEP may develop soon after the initiation of smoking, especially when starting with large quantities, and may relapse—not always—in patients who resume cigarette smoking [39, 46]. Flavoring components of smoked cigars have been suspected. In addition, the onset of IAEP seems to follow in some patients' outdoor activities or peculiar exposures, such as cave exploration, plant repotting, wood pile moving, smokehouse cleaning, motocross racing in dusty conditions, indoor renovation work, gasoline tank cleaning, explosion of a tear gas bomb, or exposure to World Trade Center dust [20, 44, 47]. Recently, cases of AEP caused by the use of electronic cigarettes [48–50] and inhalation of vaporized cannabis oil were also reported [51].

IAEP develops acutely or subacutely over less than 1 month in previously healthy individuals, with cough, dyspnea, fever, and chest pain at presentation [17, 44]. More than half of patients present with acute respiratory failure [39]. Abdominal complaints and also myalgias can occur [20]. Clinical signs include crackles or, less often, wheezes, tachypnea, and tachycardia.

Table 17.5 Diagnostic criteria for idiopathic acute eosinophilic pneumonia

1. Acute onset of febrile respiratory manifestations (≤1 month duration before consultation)
2. Bilateral diffuse opacities on chest radiography
3. Hypoxemia, with PaO_2 on room air <60 mmHg, and/or $PaO_2/FIO_2 \leq 300$ mmHg, and/or oxygen saturation on room air <90%
4. Lung eosinophilia, with >25% eosinophils on BAL differential cell count (or eosinophilic pneumonia at lung biopsy)
5. Absence of infection, or of other known causes of eosinophilic lung disease (especially exposure to a drug susceptible to induce pulmonary eosinophilia)

Imaging

Imaging of patients with IAEP is quite distinct from those with ICEP. In addition to bilateral alveolar and/or interstitial opacities (Fig. 17.4) [20, 37, 38, 44], the chest X-ray commonly shows bilateral pleural effusion and Kerley B lines [20]. The chest X-ray returns to normal within 3 weeks [20, 44], with pleural effusions being the last abnormality to disappear [20].

Typical computed tomography (CT) abnormalities include ground-glass attenuation and air space consolidation (Fig. 17.5), with poorly defined nodules. Interlobular septal thickening and bilateral pleural effusion seen in a majority of patients are highly suggestive of the diagnosis in the setting of eosinophilic pneumonia [20, 26, 37, 44, 52] (or in a patient spuriously suspected to have infectious pneumonia).

Laboratory Studies

In contrast with ICEP, peripheral blood eosinophilia is usually lacking at presentation, with white blood cell count showing increased leukocyte count with a predominance of neutrophils. However, the eosinophil count often rises within days during the course of the disease [20, 25, 44], a retrospective finding very suggestive of IAEP. When present at the presentation, peripheral eosinophilia may be associated with a milder disease status compared with those with normal eosinophil count [40, 53, 54]. Eosinophilia is also present at pleural fluid differential cell count [20] and in the sputum [25].

The IgE level may be elevated, while IgG levels may be reduced. Serum levels of thymus and activation-regulated

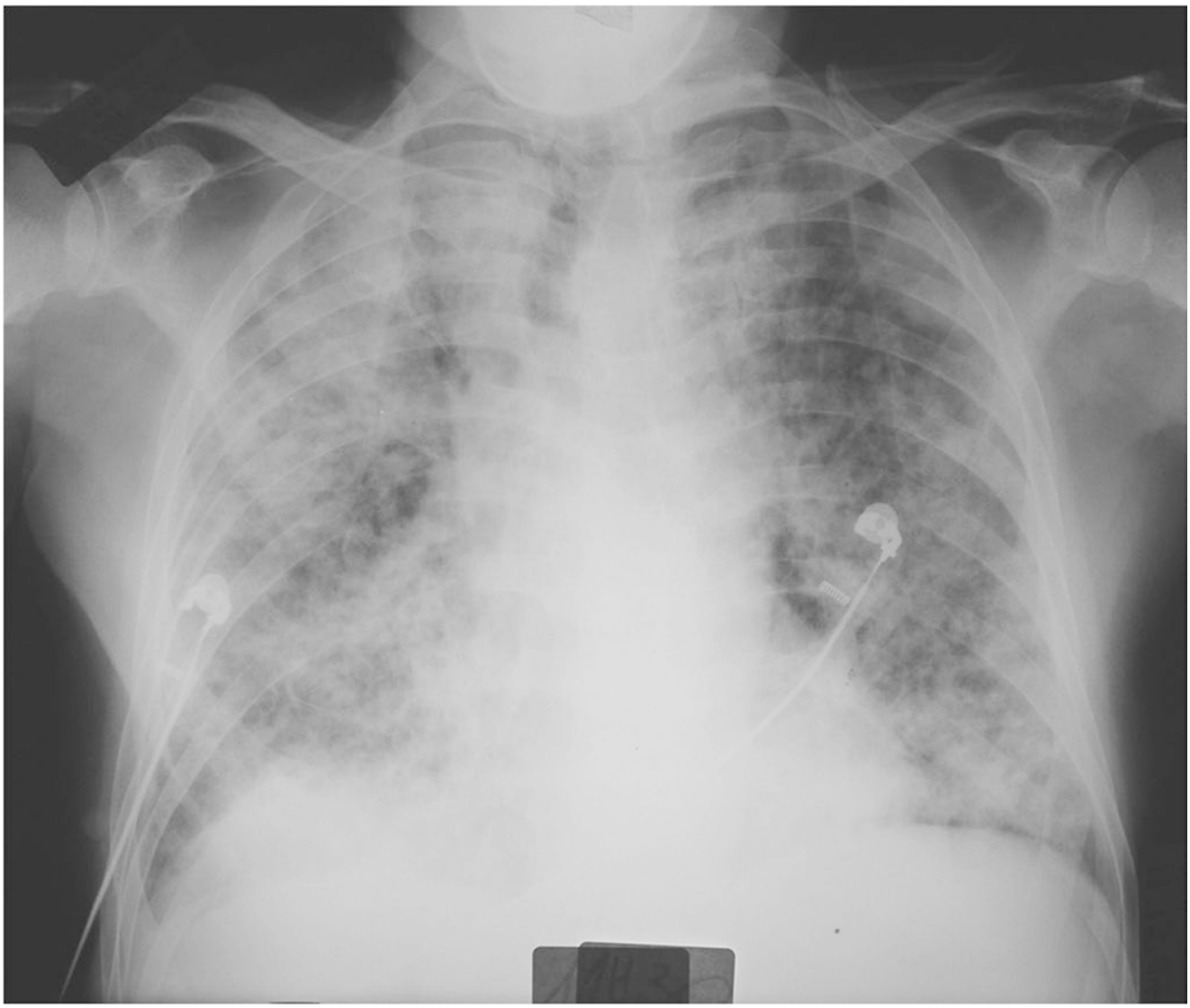

Fig. 17.4 Chest radiograph of a patient with idiopathic acute eosinophilic pneumonia and acute respiratory failure showing diffuse alveolar consolidation

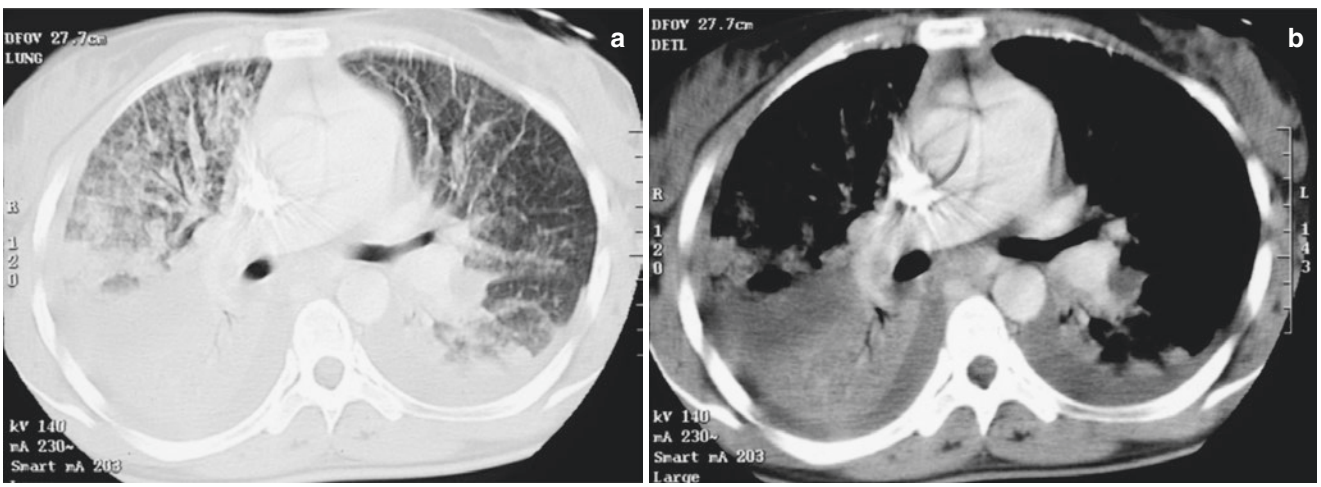

Fig. 17.5 CT scan of a patient with idiopathic acute eosinophilic pneumonia showing bilateral diffuse alveolar consolidation with air bronchograms, ground glass opacities (**a**, **parenchymal window**) and bilateral mild pleural effusion (**b**, **mediastinal window**)

chemokine (TARC/CCL17) [55] may be elevated, however, no biomarker other than eosinophil count has established clinical relevance in IAEP.

Bronchoalveolar Lavage

BAL is the key to the diagnosis of IAEP, especially in patients without blood eosinophilia at presentation. The finding of greater than 25% eosinophils at BAL obviates the need for lung biopsy, at least in immunocompetent patients. The average percentage of eosinophils at BAL differential count varies between series (37% [20] to 65% [55]), and lymphocyte and neutrophil counts can be moderately increased. Bronchoscopy may show inflamed mucosa of the trachea [56]. Importantly, systematic bacterial cultures of BAL fluid are sterile, and appropriate stainings are negative, ruling out infectious agents that can cause AEP. After recovery, eosinophilia at BAL may persist for several weeks.

Lung Function Tests

Hypoxemia may be severe in patients with IAEP, a majority of whom fit the definition of ARDS of various severity (except that there is no known clinical insult identified in IAEP) [57]. However, shock is exceptional and extrapulmonary organ failure does not occur in IAEP, in sharp contrast with ARDS.

Hypoxemia is associated with right-to-left shunting in areas with consolidation and may be refractory to breathing 100% oxygen in some patients [36, 44]. Alveolar-arterial oxygen gradient is increased [20]. Although mechanical ventilation was necessary for a majority of patients in earlier series [20, 44], more recent series have shown that the severity of IAEP is more varied than originally reported [39].

When performed in less severe cases, lung function tests show a mild restrictive ventilatory defect with normal forced expiratory volume in 1 s-to-forced vital capacity (FEV_1/FVC) ratio and reduced transfer factor. After recovery, lung function tests are generally normal, with possible ventilatory restriction in some of them [20].

Lung Biopsy

Lung biopsy or transbronchial lung biopsies are seldom necessary when BAL demonstrates alveolar eosinophilia. In older series of patients with IAEP, lung biopsy has shown acute and organizing diffuse alveolar damage together with interstitial alveolar and bronchiolar infiltration by eosinophils, intra-alveolar eosinophils, and interstitial edema [17, 20, 51, 58, 59].

Treatment and Prognosis

Exclusion of possible causes of AEP, especially infections and drugs, is key to the management of patients with AEP. Recovery of IAEP can occur without corticosteroid treatment [44, 55], and therefore improvement concomitant with corticosteroid treatment is not a diagnostic criterion of IAEP. In most patients diagnosed with IAEP, a course of corticosteroids is initiated with intravenous methyl prednisolone and later changed to oral prednisone or prednisolone that is tapered over 2–4 weeks [20]. FIO_2 may be decreased within a few hours of corticosteroid treatment in many patients initially requiring oxygen [20]; most patients are rapidly weaned from the ventilator. Clinical improvement generally begins within 3 days [39]. The chest X-ray is normalized within 1 week in 85% of patients, but mild pulmonary infiltrates and pleural effusion may still be present at CT at 2 weeks [39]. One recent study of 137 patients suggested that a treatment duration of 2 weeks may be sufficient, with an initial daily dose of 30 mg of prednisone (or 60 mg of intravenous methylprednisolone every 6 h in patients with respiratory failure) [39]. No relapse occurs after stopping corticosteroid treatment, in contrast with ICEP (Table 17.6). Because patients with peripheral blood eosinophilia at presentation tend to have milder disease, it was proposed to rapidly taper corticosteroid treatment after clinical improvement has been obtained in those subjects, leading to a very short treatment duration (median, 4 days) [60].

No significant clinical or imaging sequelae persist in the longer term. Mortality is rare despite the frequent initial presentation with acute respiratory failure. Identification of causative tobacco or environmental exposures is key to preventing rare recurrences, that in most cases are due to the resumption of cigarette smoking after a period of abstinence.

Table 17.6 Distinctive features between idiopathic chronic eosinophilic pneumonia (ICEP) and idiopathic acute eosinophilic pneumonia (IAEP)

	ICEP	IAEP
Onset	>2–4 weeks	<1 month
History of asthma	Yes	No
Smoking history	10%	2/3, with often recent initiation
Respiratory failure	No	Usual
Initial blood eosinophilia	Yes, on admission	No (delayed)
BAL eosinophilia	>25% (generally >40%)	>25%
Chest imaging	Homogeneous peripheral airspace consolidation	Bilateral patchy areas of ground glass attenuation, airspace consolidation, interlobular septal thickening, bilateral pleural effusion
	Predominance in upper lobes and lung periphery	
Relapse	Yes, possibly multiple	No

Eosinophilic Granulomatosis with Polyangiitis

History and Nomenclature

The first reliable case of EGPA (ex Churg-Strauss syndrome) was reported by Lamb in 1914 [61]. Churg and Strauss described in 1951 [62] the eponymous syndrome of "allergic granulomatosis, allergic angitis, and periarteritis nodosa," mainly from autopsied cases. In the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis [63], CSS was included in the group of small vessel vasculitides. The nomenclature of the systemic vasculitides was revised in 2012 at the international Chapel Hill consensus conference [64], and the terminology of CSS was replaced by EGPA. As antineutrophil cytoplasmic antibodies (ANCA) are present in about 40% of the cases, EGPA belongs to the pulmonary ANCA-associated vasculitides, together with microscopic polyangiitis and granulomatosis with polyangiitis, and together with single organ ANCA-associated vasculitis.

EGPA is defined as an eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia [64]. The disease may be confined to a limited number of organs especially the upper or lower respiratory tract [64], with reported cases of histologically-confirmed EGPA localized to the lung [13]. The terminology of EGPA underscores that it is indeed a vasculitis, although not all patients have robust criteria of documented systemic vasculitis or ANCA [65]. Furthermore, some cases of pulmonary eosinophilic vasculitis are distinct from EGPA [66]. The current terminology and classification likely require further refinement.

Pathology

The pathologic lesions of EGPA (CSS) observed in series published over the last 20 years [67, 68] only rarely comprise all the characteristic features on biopsies from organs other than the lung, which is now rarely biopsied [13]. The diagnosis is made earlier in the course of the disease, often before overt vasculitis has developed, characterized histopathologically by eosinophilic infiltration of the tissues and often perivascular eosinophils but without vasculitis. In cases with overt EGPA, typical histopathologic features include vasculitis (necrotizing or not, involving mainly the medium-sized pulmonary arteries), granulomatous eosinophilic infiltration, and extravascular granuloma with palisading histiocytes and giant cells. When present, eosinophilic pneumonia in EGPA is similar to ICEP.

Clinical Features

EGPA is a very rare systemic disease, with no sex predominance, predominating in adults younger than 65 [65, 69–84], with cases occasionally reported in children and adolescents [85, 86]. Asthma occurs at a mean age of about 35 years [69] in patients with EGPA, preceding the onset of vasculitis by 3–9 years [69, 71, 72, 75, 82]; therefore the mean age at diagnosis of EGPA ranges from 38 to 49 years [69, 75]. The interval between asthma and the onset of vasculitis may be much longer in rare cases [71], or they may be contemporaneous [75]. Asthma is generally severe, and frequently requires oral corticosteroids; its severity typically increases progressively until the vasculitis develops, but it may attenuate when the vasculitis flourishes (possibly as a result of corticosteroids) and further increase once the vasculitis recedes [69, 71, 82, 87].

Chronic rhinitis (75% of cases) [69], relapsing paranasal sinusitis (60%) [72], and nasal polyposis with eosinophilic infiltration at histopathology are frequent [88, 89]. Crusty rhinitis may be present, however, it is much less severe in EGPA than in granulomatosis with polyangiitis. Septal nasal perforation and saddle nose deformation are exceedingly rare.

Asthenia, weight loss, fever, arthralgias, and myalgias often herald the onset of systemic vasculitis.

Heart damage in EGPA is undoubtedly a major source of morbidity and mortality, although its onset is often insidious and asymptomatic and diagnosed only when left ventricular failure and dilated cardiomyopathy have developed, possibly leading to cardiac failure or sudden death [69–72, 75, 90]. Heart involvement mostly results from eosinophilic myocarditis, and rarely from arteritis of the larger coronary arteries [91, 92]. Although marked improvement usually occurs with corticosteroid treatment, heart involvement in EGPA may require heart transplantation, with possible recurrence of eosinophilic vasculitis in the transplanted heart. A systematic cardiac evaluation is therefore warranted in any patient with suspected EGPA, generally including electrocardiogram, echocardiography, serum level of troponin, and N-terminal pro-brain natriuretic peptide. Magnetic resonance imaging (MRI) of the heart is the preferred method to confirm heart involvement, showing late enhancement of the myocardium [93–95]; however, it may be difficult to differentiate irreversible scar lesions from active inflammation requiring intense immunosuppression, and incidental findings from clinically relevant myocardial involvement. Treatment decisions are eventually based on critical clinical evaluation, taking into account results from several investigations, including electrocardiogram, echocardiography, troponin levels, and possibly a combination of cardiac MRI and Positron emission tomography. In addition to myocardial involvement, asymptomatic pericarditis with limited effusion at echocardiography is common, with rare cases of tamponade, and the risk of venous thromboembolic events [96] is increased in patients with EGPA. Endomyocardial involvement (typically seen in idiopathic HES) is uncommon in EGPA.

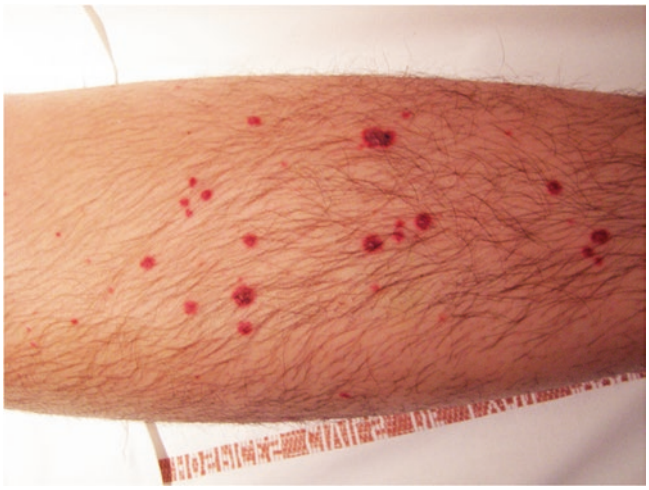

Fig. 17.6 Palpable purpura of the forearm in a patient with eosinophilic granulomatosis with polyangiitis

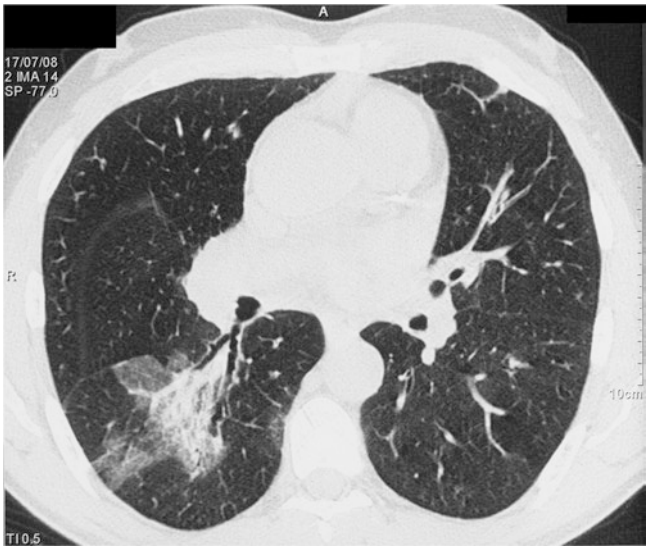

Fig. 17.7 CT scan of a patient with eosinophilic granulomatosis with polyangiitis showing airspace consolidation and ground glass opacity in the right lower lobe

Virtually all organs can be involved by EGPA. Mononeuritis multiplex, present in 77% of patients [72], is the most frequent and the most typical of peripheral neurologic involvement in EGPA, which may also consist of asymmetrical polyneuropathy in the lower extremities, or rarely cranial nerve palsies or central nervous system involvement [97]. Digestive tract involvement (31% of cases [72]) consists of isolated abdominal pain, and less frequently intestinal or biliary tract vasculitis, diarrhea, ulcerative colitis, gastroduodenal ulcerations, perforations (esophageal, gastric, intestinal), digestive hemorrhage, or cholecystitis. Cutaneous lesions (50% of patients [72]) mainly consist of palpable purpura of the extremities (Fig. 17.6), subcutaneous nodules (especially of the scalp and extremities), erythematous rashes, and urticaria. Renal involvement (about 25% of cases) may present as mild glomerulonephritis or glomerular hematuria [72]; however, renal failure is rare contrasting with the other ANCA-associated vasculitides [98].

Imaging

Pulmonary opacities corresponding to eosinophilic pneumonia are present on chest X-ray in a majority of patients with EGPA (37% [72] to 72% [69, 99]) and consist of ill-defined opacities, sometimes migratory, transient, and of varying density [69, 71, 100, 101]. In contrast to GPA, pulmonary cavitary lesions are exceptional. The chest X-ray may remain normal throughout the course of the disease. Mild pleural effusion and phrenic nerve palsy can be observed.

On thin-section chest CT, pulmonary abnormalities can schematically be separated according to whether they predominate in the airspaces corresponding to eosinophilic pneumonia, or in the airways corresponding to bronchiolar and bronchial involvement [101–103]. Airspace abnormalities or "infiltrates" consist of ill-defined opacities, with a density varying from ground glass attenuation to airspace consolidation (Fig. 17.7). They typically predominate in the lung periphery and upper zones of the lung, or have a random distribution, and can be migratory as in ICEP [26, 82, 100, 101]. Airway abnormalities include centrilobular nodules, bronchial wall thickening, and occasionally bronchiectasis or tree-in-bud pattern [26, 27, 82, 101]. Interlobular septal thickening, hilar or mediastinal lymphadenopathy, pleural effusion, and pericardial effusion [26, 100, 101] are less commonly found. In one study, centrilobular nodules were more frequent in EGPA than in patients with ICEP [27]. However, EGPA is difficult to differentiate from other causes of eosinophilic lung diseases on the basis of HRCT imaging [26]. Importantly, pleural effusion may arise due to either inflammatory eosinophilic exudate directly related to EGPA or a transudate caused by cardiomyopathy.

Laboratory Studies

Peripheral blood eosinophilia is a major feature of EGPA, with typical eosinophil counts between 5 and 20 × 10^9/L, although higher values are occasionally found [69, 71, 72, 82]. Blood eosinophilia usually parallels disease activity, and disappears within hours after the initiation of corticosteroid treatment [82]. Eosinophilia, sometimes greater than 60%, is also found on BAL differential cell count and in the pleural fluid when present.

Although EGPA belongs to the group of ANCA-associated vasculitides, ANCAs are present in only about 40% of patients. ANCAs in EGPA are mainly perinuclear (p-ANCA) with myeloperoxidase specificity, and more rarely are cytoplasmic ANCAs (c-ANCA) with proteinase 3 specificity [65,

Table 17.7 Distinct phenotypes of eosinophilic granulomatosis with polyangiitis

	Vasculitic phenotype	Tissular disease phenotype
Respective frequency	~40%	~60%
ANCA	Present (mostly p-ANCA with anti-MPO specificity)	Absent
Predominant clinical and histopathologic features	Glomerular renal disease	Cardiac involvement (eosinophilic myocarditis)
	Peripheral neuropathy	
	Purpura	Fever
Predominant histopathologic features	Biopsy-proven vasculitis	Eosinophilic pneumonia

ANCA antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *p-ANCA* perinuclear antineutrophil cytoplasmic antibody
Adapted from references [77, 78]

72, 75, 77, 78, 80]. ANCA status characterizes two distinct clinical phenotypes in EGPA (Table 17.7), albeit with some overlap [65, 77–80, 104, 105]. Patients with ANCA have a vasculitic phenotype, with more frequent glomerular renal disease, peripheral neuropathy, palpable purpura, and biopsy-proven vasculitis. Patients without ANCA have a tissue phenotype of disease with more frequent eosinophilic myocarditis and eosinophilic pneumonia, which may correspond to a variant of the HES with systemic manifestations. Interestingly, genetic predisposition affects the phenotype of EGPA. The vasculitic phenotype of EGPA is more frequent in individuals carrying the major histopathology complex DRB4 allele, whereas the IL-10-3575/1082/592 TAC haplotype is associated with the ANCA-negative EGPA phenotype.

The serum IgE level, erythrocyte sedimentation rate, C-reactive protein level, and serum levels of IgG4, and other biomarkers are increased although none is validated as a diagnostic or prognostic EGPA biomarker. Anemia is common. High levels of urinary EDN may represent an activity index of disease. ANCAs are present in the sputum of patients with EGPA [106]; however, measurement of ANCAs in the sputum is not recommended in clinical practice.

Pathogenesis

EGPA is both a hypereosinophilic condition and an ANCA-associated systemic vasculitis, comprising two distinct yet overlapping pathogenic mechanisms [107]. ANCA-associated EGPA is considered an autoimmune process involving a Th2-mediated inflammatory response. A genetic predisposition within the major histopathology complex has been demonstrated in relation to EGPA, with the presence of ANCA, and with the clinical phenotype of the disease. Similarly, in patients without ANCA, another genetic predisposition was reported within the promoter of IL-10, an important anti-inflammatory cytokine. Familial EGPA has been reported, and the phenotype of EGPA may be affected by genetic predisposition.

EGPA is considered an autoimmune process involving T-cells, endothelial cells, and eosinophils. Defects have been identified in regulatory CD4+ CD25+ or CD4+ CD25− T-cell lymphocytes (producing IL-10 and IL-2) that may influence the progression of the disease, and support an immunological hypothesis of disease. Furthermore, clonal CD8+/Vβ+ T-cell expansions with effector memory phenotype and expressing markers of cytotoxic activity were found in peripheral blood lymphocytes, as well as T-cell receptor-Cβ gene rearrangement.

Contrary to common belief, evidence of allergy demonstrated by specific IgE together with a corresponding clinical history is present in less than one-third of patients [82]. When present in EGPA, allergy mainly consists of perennial allergies to Dermatophagoides, whereas seasonal allergies are less frequent than in the general asthmatic patient [108].

A variety of factors were historically reported to trigger or serve as adjuvant factors in the onset of EGPA, including some vaccines, desensitization protocols [109], fungal infections, smoked cocaine, and a variety of drugs (sulfonamides used together with antiserum, diflunisal, macrolides, diphenylhydantoin, mesalazine, propylthiouracil, masitinib, immune checkpoint inhibitors). Leukotriene-receptor antagonists (montelukast, zafirlukast, pranlukast) have been suspected to be involved in the development of EGPA, although their role is controversial [34, 75, 110–114]. The association between EGPA and leukotriene receptor antagonists may be coincidental, corresponding to EGPA flares related to reducing oral or inhaled corticosteroid doses in patients with smoldering EGPA; however, a direct causal relationship cannot be totally excluded [110, 112, 114, 115]. Many authors advocate for the avoidance of leukotriene receptor antagonists in patients with asthma, eosinophilia, and/or established or smoldering extrapulmonary manifestations. The onset of EGPA in asthmatic patients treated with inhaled corticosteroids [116], or with omalizumab, an anti-IgE antibody, is probably due to the reduction in corticosteroids [34, 117–122].

Diagnosis

The classical description of EGPA follows three stages: asthma and rhinitis; tissue eosinophilia (such as a pulmonary disease resembling ICEP); and extrapulmonary eosinophilic disease with vasculitis [65, 82]. Diagnosing EGPA may be challenging in patients with early disease corresponding to the so-called *formes frustes* [123], who often already receive oral corticosteroids for asthma, thereby masking the underlying smoldering vasculitis. The diagnosis is more straightforward at a later stage of disease with overt systemic

manifestations; however, it is extremely important that the diagnosis be established before severe organ involvement (especially cardiac) is present.

There are currently no established diagnostic criteria for EGPA. Lanham and associates [69] have proposed three diagnostic criteria including (1) asthma, (2) eosinophilia exceeding 1.5×10^9/L, and (3) systemic vasculitis of two or more extrapulmonary organs. These criteria do not include ANCAs, however, which when present certainly contribute to the diagnosis. Classification criteria (which are not *diagnostic* criteria) have been proposed by the American College of Rheumatology [124] and were recently updated by the American College of Rheumatology and the European Alliance of Associations for Rheumatology (Table 17.8) [128]. These criteria are validated for use in research for the classification as EGPA, in patients with a confirmed diagnosis of small- or medium-vessel vasculitis, and after excluding mimics of vasculitis, with excellent specificity. They are not validated, however, and cannot be readily used for the clinical diagnosis of EGPA in patients not yet diagnosed with systemic vasculitis. Inclusion criteria used in a recent trial may be used as diagnostic criteria [125]; however, they too need proper validation. Working diagnostic criteria including ANCA are shown in Table 17.8 [129].

Although a pathologic diagnosis is desirable and can be obtained from the skin, nerve, or muscle [72], it is not mandatory in patients with characteristic features of EGPA. Because cutaneous lesions are easy to access (when not involving the face), a skin biopsy is commonly performed to obtain pathologic evidence of vasculitis when they are present (Clinical Vignette). Conversely, lung biopsy either transbronchial or video-assisted is seldom necessary.

Table 17.8 Diagnostic and classification criteria of eosinophilic granulomatosis with polyangiitis

Reference	Criteria
Lanham and colleagues [69]	• Asthma
	• Eosinophilia
	• Evidence of vasculitis involving at least two organs
American College of Rheumatology[a] [124]	• Asthma
	• Eosinophilia >10%
	• Mononeuropathy, or polyneuropathy
	• Pulmonary infiltrates, nonfixed
	• Paranasal sinus abnormality
	• Extravascular eosinophil infiltration on biopsy findings
2012 Chapel Hill Consensus conference definition [64]	• Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract
	• Necrotizing vasculitis predominantly affecting small to medium vessels
	• Associated with asthma and eosinophilia
	• ANCA is more frequent when glomerulonephritis is present
Diagnostic criteria used in trial NCT02020889 [125]	• History or presence of: asthma plus eosinophilia (>1.0×10^9/L and/or >10% of leukocytes) plus at least two of the following additional features of EGPA
	• A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation
	• Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)
	• Pulmonary infiltrates, non-fixed
	• Sino-nasal abnormality
	• Cardiomyopathy (established by echocardiography or MRI)
	• Glomerulonephritis (haematuria, red cell casts, proteinuria)
	• Alveolar hemorrhage (by bronchoalveolar lavage)
	• Palpable purpura
	• ANCA positive (MPO or PR3).
Diagnostic criteria used by these authors[b] [126, 127]	1. Asthma
	2. Peripheral blood eosinophilia >1500/mm^3 and/or alveolar eosinophilia >25%
	3. Extrapulmonary clinical manifestations of disease (other than rhinosinusitis), with at least one of the following:
	(a) systemic manifestation typical of the disease: mononeuritis multiplex; or cardiomyopathy confidently attributed to the eosinophilic disorder; or palpable purpura
	(b) any extrapulmonary manifestation with histopathological evidence of vasculitis as demonstrated especially by skin, muscle, or nerve biopsy
	(c) any extrapulmonary manifestation with evidence of ANCA with antimyeloperoxidase or antiproteinase 3 specificity

[a]Diagnosis is probable when four of the six criteria are present (sensitivity of 85%, specificity of 99.7%); these are classification criteria that may be used when the diagnosis of systemic vasculitis has been established by histopathology

[b]When a single extrapulmonary manifestation attributable to the systemic disease is present, disease may be called "forme fruste of EGPA"

Differential Diagnosis

Differentiating EGPA from the other ANCA-associated vasculitides and the other eosinophilic syndromes can be difficult. ANCA-negative EGPA without typical polyangiitis features and "formes frustes" (often consisting of cases in which the disease has been controlled to a greater or lesser extent by corticosteroids given for asthma) may overlap with unclassified systemic eosinophilic disease especially ICEP with minor extrathoracic symptoms. ICEP may also progress to EGPA. Furthermore, pathological features of mild non-necrotizing vasculitis are common in patients with ICEP [11]. Cases of EGPA strictly limited to the lung were reported and were established by lung biopsy performed due to atypical, corticosteroid-dependent, courses of eosinophilic pneumonia [13]. EGPA can also overlap with idiopathic HES. When present, ANCA or the finding of vasculitis and granulomas on biopsy contribute to the diagnosis of EGPA, whereas molecular biology or c-ANCA with proteinase-3 specificity may argue in favor of a diagnosis of idiopathic HES or GPA, respectively.

Idiopathic systemic eosinophilic vasculitis [12] is a recently described entity. Pathologically, the vasculitis, which may be necrotizing or not, differs from that of EGPA, without granulomas. By definition, patients do not have a history of asthma. Lung involvement may occur [66], although it has not yet been described in detail. Although idiopathic systemic eosinophilic vasculitis is distinct from EGPA, it may be part of a common spectrum [66].

Treatment and Prognosis

Treatment of EGPA is based on corticosteroids, which suffice in a large number of cases [69, 130–132]. In the most severe cases, treatment is initiated with methylprednisolone pulses, for 1–3 days, followed by oral corticosteroids, usually started with 1 mg/kg/day of prednisone, and continued for several months with progressive reduction of doses. Relapses are common as corticosteroids are tapered or after treatment has been discontinued, and may present as relapses of the systemic vasculitis (usually accompanied by increased peripheral blood eosinophilia greater than 1×10^9), or more frequently as remitting or persistent difficult asthma that may require long-term low-dose oral corticosteroids despite optimal inhaled asthma therapy [82, 87].

Patients with poor prognostic factors at the onset that could result in mortality or severe morbidity should receive intravenous pulses of cyclophosphamide therapy in addition to corticosteroids (three intravenous infusions of 0.6 g/m^2 intravenously each at Day 1, 15, 30; then three additional infusions of 0.7 g/m^2 every 3 weeks). Intravenous cyclophosphamide is preferred to oral administration as it is better tolerated. The dose of cyclophosphamide may be reduced to 0.5 g in individuals older than 65 years [133]. Although 12 cyclophosphamide pulses are better able to control the disease, a 6-pulse regimen is generally preferred when complete remission of the vasculitis is obtained. Four factors have been associated with a poor prognosis in patients with EGPA in a study of patients with either polyarteritis nodosa or EGPA, namely age >65 years, cardiac symptoms based on easily detectable clinical parameters, gastrointestinal involvement, and renal insufficiency with stabilized peak creatinine >150 μmol/L, whereas ear, nose and throat symptoms were associated with a lower risk of death from EGPA ("revisited five-factor score") [134]. Immunosuppressive therapy with cyclophosphamide is therefore warranted in patients with a five-factor score >1 and especially those with heart failure [135, 136]. Cardiomyopathy is indeed the main predictor of mortality [79], especially in the case of heart failure [135]. In addition, severe alveolar hemorrhage, eye involvement (e.g. scleritis), and/or fulminant mononeuritis multiplex also warrants the use of immunosuppressants. Disease control is improved by a combination of immunosuppressants with corticosteroids, with the caveat of a higher risk of infections.

Once remission has been achieved, prolonged maintenance therapy is necessary to prevent relapses. In the absence of criteria of poor prognosis, it generally consists of glucocorticoids alone, in tapering doses [137]. Immunosuppressive therapy, especially azathioprine or methotrexate, is occasionally used as a corticosteroid-sparing agent in this situation, particularly in subjects who require 10 mg/day of prednisone or more, however, it may now be less frequently used due to the availability of eosinophil targeted therapy. In patients with poor prognostic criteria, maintenance therapy is generally based on azathioprine for 18–24 months. Mycophenolate mofetil could be less effective than azathioprine to prevent relapses [138], but methotrexate 0.25 mg/kg/week is an alternative to azathioprine [139].

Mepolizumab, a human, a monoclonal antibody that binds to IL-5 and prevents its interaction with its receptor on the eosinophil surface, consistently reduces eosinophil cell counts in peripheral blood and improves severe eosinophilic asthma [140–144]. The efficacy and safety of mepolizumab were evaluated in a phase 3 randomized trial as add-on therapy versus placebo in subjects with relapsing or refractory EGPA [125], in many patients due to difficult to control asthma. As compared to placebo, mepolizumab (300 mg every 4 weeks) led to an increased proportion of patients achieving remission, an increased duration of remission, a lower rate of relapse, and a lower average daily dose of oral corticosteroids [125]. Mepolizumab is indicated as an adjunct therapy in subjects with relapsing or refractory EGPA, however many questions remain regarding its optimal use and timing in EGPA. Observational data confirm the efficacy of mepolizumab in EGPA [145, 146], and further suggest that mepolizumab (100 or 300 mg every 4 weeks)

may further be beneficial in cases with persistent severe asthma when the vasculitis is in remission [145, 147].

Reslizumab, another monoclonal antibody against IL-5, and benralizumab, a monoclonal antibody directed against the alpha subunit of IL-5 receptor, both have demonstrated a sparing effect of oral corticosteroids in prospective open-label pilot studies, each in ten patients with EGPA [148, 149]. The efficacy and safety of these drugs in EGPA warrant further study.

The optimal sequence and potential combinations of drugs for patients with EGPA remain to be determined. The 2021 guidelines of the American College of Rheumatology/Vasculitis Foundation recommend first-line treatment with pulse intravenous corticosteroids, high-dose corticosteroids, cyclophosphamide, or rituximab in patients with active severe EGPA, and oral corticosteroids combined with mepolizumab, methotrexate, azathioprine, mycophenolate mofetil, or rituximab, in patients with active non-severe EGPA [150]. Maintenance therapy once remission has been achieved may consist of methotrexate, azathioprine, or mycophenolate mofetil [150].

The anti-IL4/13 monoclonal antibody dupilumab may trigger hypereosinophilia with sudden deterioration of asthma, eosinophilic tissue infiltration, and EGPA-like symptoms in patients previously treated or not with anti-IL-5/IL-5R antibodies, and should therefore be used with caution when the diagnosis of EGPA is contemplated [151, 152].

The anti-IgE omalizumab has been used successfully to treat persistent asthma in patients with EGPA [153]; careful clinical monitoring is warranted because omalizumab does not control the systemic disease. Observational data suggest that rituximab may be useful [147]. In addition, some selected cases of severe EGPA refractory to corticosteroids and/or cyclophosphamide may respond to subcutaneous interferon-alfa, high-dose intravenous immunoglobulins, or cyclosporin A. The low level of evidence for these approaches is low, however.

Long-Term Outcome

Long-term follow-up is warranted due to the risk of relapse of the vasculitis, which is not prevented by cytotoxic agents, and is higher in patients with ANCA [79] and lower in those with baseline eosinophils >3.0 × 10^9/L [136]. The 5-year overall survival in EGPA is currently greater than 90% [65, 79, 81], and as high as 97% were alive in those without poor-prognosis factors [154]. Mortality is associated with disease severity. Most deaths during the first years of treatment are due to cardiac involvement [79, 155], gastrointestinal bleeding, renal insufficiency, or central nervous system involvement [130, 134].

Long-term morbidity is related to side effects of oral corticosteroids [81, 82, 154], and to frequent uncontrolled asthma with airflow obstruction (that in some cases may still be partly reversible with increased oral corticosteroid treatment [156]) despite corticosteroids and inhaled therapy [82, 87, 156–158].

Hypereosinophilic Syndrome

Definition

The "idiopathic" HES was historically defined in 1975 by Chusid and coworkers [159] as (1) a persistent eosinophilia greater than 1.5 × 10^9/L for longer than 6 months, or death before 6 months associated with the signs and symptoms of hypereosinophilic disease, (2) a lack of evidence for parasitic, allergic, or other known causes of eosinophilia, and (3) presumptive signs and symptoms of organ involvement, including hepatosplenomegaly, organic heart murmur, congestive heart failure, diffuse or focal central nervous system abnormalities, pulmonary fibrosis, fever, weight loss, or anemia.

The definition of HES was revised in a consensus statement [23], now requiring the following three criteria:

- Absolute blood eosinophil count ≥1500/μL on two examinations (with an interval of 1 month or more) and/or tissue hypereosinophilia defined by the following:
  - Percentage of eosinophils in the bone marrow section exceeds 20% of all nucleated cells and/or
  - Pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or
  - Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils).
- Organ damage and/or dysfunction attributable to tissue hypereosinophilia, and
- Exclusion of other disorders or conditions as a major reason for organ damage.

HES is further divided into variants [23]: a hereditary (familial) HES variant, HES of undetermined significance, primary (clonal/neoplastic) HES produced by apparently clonal (neoplastic) eosinophils, and secondary (reactive) HES related to an underlying condition/disease in which eosinophils are considered non-clonal cells and HES is considered cytokine-driven in most cases.

Conditions such as ICEP and IAEP characterized by hypereosinophilia (as defined above) and clinical manifestations limited to a single organ are classified as an eosinophil-associated single-organ disease [23]. This section will mainly review pulmonary manifestations associated with clonal/neoplastic HES and reactive HES.

Pathogenesis

HES may result from clonal cell proliferation, involving either the lymphocyte lineage in the "lymphocytic variant"

of HES whereby clonal lymphocytes produce eosinophilopoetic chemokines, or the eosinophil cell lineage itself in chronic eosinophilic leukemia (the "myeloproliferative variant" of HES). In such cases, the HES may be considered a premalignant T-cell disorder [160, 161] or chronic leukemia, respectively. The term *idiopathic* is used to describe cases that cannot be classified in either category, and further innovative diagnostic tools will likely contribute in the future to differentiate these cases from other causes of eosinophilia of determined cause.

In the clonal/neoplastic HES variant, also called chronic eosinophilic leukemia (formerly, "myeloproliferative variant" of HES), an interstitial chromosomal deletion of a region in the long arm of chromosome 4 (q12) is causing a fusion protein by fusion of *FiplLl–PDGFR-α*, with the constitutive activation of the tyrosine kinase domain. Patients frequently present with hepatomegaly, splenomegaly, mucosal ulcerations, severe cardiac manifestations resistant to corticosteroid treatment, anemia, thrombocythemia, increased serum vitamin B_{12}, leukocyte alkaline phosphatase, and serum tryptase, circulating leukocyte precursors, and pronounced mastocytosis (lacking *KIT* mutations). Cutaneous manifestations are infrequent. Because the deletion is not detectable by karyotype analysis [162, 163], an analysis of chromosomal deletion using FISH probes to the gene *CHIC2* encompassed in the deleted sequence, and of the expression of the *FiplLl–PDGFR-α* fusion gene is required for the diagnosis. The tyrosine kinase activity of the fusion protein is inhibited by imatinib, which proved efficient in treating HES in patients refractory to corticosteroids, hydroxyurea, and/or interferon-α. Clonal eosinophilia in patients presenting with clinical features of HES can also be related to other uncommon, mutations in *PDGFRA*, *PDGFRB*, *KIT*, *BCR/ABL1*, *FGFR1*, or *JAK2* [164].

Patients with the reactive HES variant have an underlying inflammatory, neoplastic, or other disease or condition known to cause hypereosinophilia through the production of eosinophilopoietic cytokines. Specifically, chemokines (especially IL-5, but also IL-3) produced by clonal Th2 lymphocytes bearing clonal rearrangement of the TCR with an aberrant immunologic phenotype (such as $CD3^-$ $CD4^+$) promote the accumulation of eosinophils. An underlying hematopoietic neoplasm producing clonal eosinophils has to be excluded by means of histopathologic, cytogenetic, and molecular analyses. However, reactive HES can occur in hematopoietic neoplasms, such as in Hodgkin lymphoma, T-cell lymphoma, or B-lymphoblastic leukemia/lymphoma carrying certain molecular defects [23], a situation often referred to as the lymphoid variant of HES [23]. Lymphocyte phenotyping by flow cytometry to detect a phenotypically aberrant T-cell subset, and analysis of the rearrangement of the TCR genes in search of T-cell clonality in the peripheral blood (and possibly bone marrow), are therefore key to the diagnosis. Demonstration of increased IL-5 expression from cultured T-cells can also contribute to the diagnosis. Papules or urticarial plaques infiltrated by lymphocytes and eosinophils (and rarely, a cutaneous T-cell lymphoma or the Sezary syndrome) are frequently present. Serum levels of IL-5, TARC, and total IgE are increased but nonspecific.

Clinical and Imaging Features

The pulmonary involvement in patients with eosinophilia of clonal origin has not been studied specifically in the different variants of the HES. Most data available derive from older studies, in which the HES occurs much more commonly in men than in women (9:1), usually between 20 and 50 years, with insidious onset or incidental discovery of peripheral eosinophilia [165]. The mean eosinophil count at presentation was 20.1×10^9/L in one series [166], with occasionally extremely high values in excess of 100×10^9/L [159].

Lung or pleural involvement is uncommon in the reactive/lymphocytic variant of the HES [160, 161]. However, pulmonary involvement was reported at chest CT in about 40% of patients with clonal/neoplastic HES variant (formerly chronic eosinophilic leukemia) [159, 165].

Patients present with weakness and fatigue (26%), cough (24%), dyspnea (16%) [165], or asthmatic symptoms (25%) [167]. Morbidity and mortality in HES are driven by cardiovascular involvement, with characteristic endomyocardial fibrosis [165] (which differs from the eosinophilic myocarditis seen in EGPA), causing dyspnea, congestive heart failure, mitral regurgitation, cardiomegaly [165], and typical features at echocardiography [168]. The other manifestations of HES include neurologic manifestations (thromboembolic, central nervous system dysfunction, peripheral neuropathies), and cutaneous manifestations (erythematous pruritic papules and nodules, urticaria, and angioedema).

Respiratory manifestations are generally of mild severity, with rare eosinophilic pneumonia if any [167]. Chest CT may show pleural effusion, pulmonary emboli, small nodules, occasionally a halo of ground-glass attenuation, and focal areas of ground-glass attenuation mainly in the lung periphery [26, 169]. Notably, imaging features corresponding to eosinophilic lung involvement must be differentiated from those related to pulmonary edema resulting from cardiac involvement. Chronic dry cough can be remarkable and may be a presenting or the only feature [170–172].

Laboratory Studies

Blood eosinophilia is typically very high, exceeding $3–5 \times 10^9$/L, with higher values than in other eosinophilic lung diseases. Eosinophilia may be only mild at BAL, however suggesting that eosinophilia may be compartmentalized. Elevated serum levels of mast cell tryptase, and dysplastic mast cells may be present in the bone marrow, with some patients meeting minor criteria for systemic mastocytosis.

Treatment and Prognosis

In patients with the clonal/neoplastic HES variant (chronic eosinophilic leukemia), imatinib is the first-line therapy, with a more frequent response when the Fip1L1–PDGFR-α fusion protein is present [162–164, 173–175]. Imatinib should initially be associated with corticosteroids. Testing for the presence of FIP1L1-PDGFRA is recommended every 3–6 months in patients who require chronic imatinib therapy to avert relapses [176]. Long-term continuation of treatment is required in some patients to maintain remission, with possible tapering of the dose, whereas imatinib can be stopped without relapse in others [175]. Chemotherapeutic agents (hydroxyurea, vincristine, etoposide), cyclosporin A, and interferon-α either as monotherapy or in association with hydroxyurea, may be beneficial in some refractory cases.

In patients with the reactive "lymphocytic variant" of HES, corticosteroids remain the mainstay of treatment, although a response is obtained in only about half of them [164]. Mepolizumab, an anti-IL5 antibody, is beneficial as a corticosteroid-sparing agent in HES patients negative for the *FiplLl–PDGFR-α* fusion gene and requiring 20–60 mg/day of prednisone to maintain a stable clinical status and a blood eosinophil count of less than 1×10^9/L [177–179].

The long-term prognosis of HES has improved considerably, with a 3-year survival of only 12% in the first published series [159], to only one death in a recent series of 44 cases [175]. Further improvement in the long-term outcome and survival with this condition can be anticipated from recent advances in gene molecular biology that rapidly translate into innovative therapies.

Idiopathic Hypereosinophilic Obliterative Bronchiolitis

Hypereosinophilic obliterative bronchiolitis is a recently individualized entity [180], currently defined by provisional working criteria (Table 17.9), associating demonstration of bronchiolitis, of peripheral blood and/or alveolar eosinophilia, and persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids. Demonstration of bronchiolitis may be obtained by lung biopsy [180–182] and/or HRCT showing direct signs of bronchiolitis (e.g. centrilobular nodules and branching opacities) [180, 183] (Fig. 17.8). Hypereosinophilic obliterative bronchiolitis can be idiopathic, but may also occur in the setting of EGPA, ABPA, drug-induced eosinophilic lung disease (such as minocycline), and possibly in severe asthma [180].

Table 17.9 Working diagnostic criteria for hypereosinophilic obliterative bronchiolitis [180]. All three criteria are required. Hypereosinophilic obliterative bronchiolitis may be secondary to various conditions including EGPA, ABPA, or drug-induced eosinophilic lung disease

Peripheral blood and/or BAL	Blood eosinophil cell count >1 × 10^9/L and/or bronchoalveolar lavage eosinophil count >25%
Pulmonary function tests	Persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids
Demonstration of bronchiolitis	Eosinophilic bronchiolitis at lung biopsy and/or direct signs of bronchiolitis (centrilobular nodules and branching opacities) on computed tomography

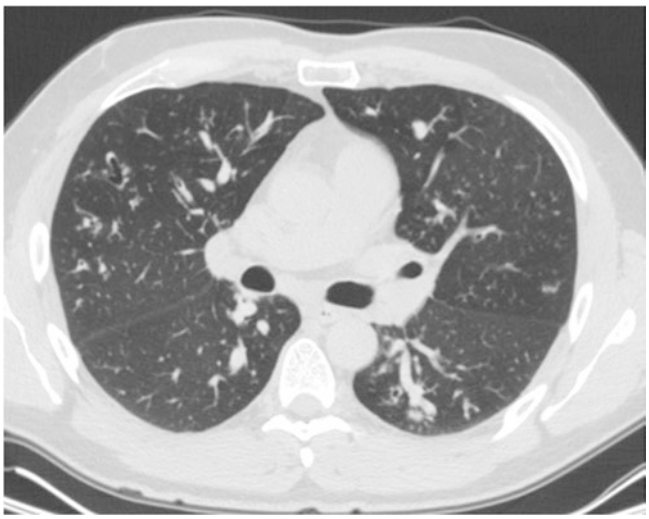

Fig. 17.8 CT scan of a patient with idiopathic hypereosinophilic bronchiolitis showing bronchiectasis in the right middle lobe and mucoid impaction in the left lower lobe

Patients report cough and exercise dyspnea but generally do not present with intermittent asthma symptoms or wheezes. The blood eosinophil cell count (with a mean value of 2.7×10^9/L), and the mean eosinophil differential percentage at BAL (with a mean value of 63%) are elevated [180]. Airflow obstruction is often severe but reversible in all cases with the initiation of oral corticosteroid therapy or increasing its daily dose, however, clinical and functional manifestations often recur when the daily dose of oral prednisone is tapered to less than 10–15 mg. Mepolizumab or benralizumab may be beneficial [184–187] however experience in this indication is very limited.

Unrecognized untreated hypereosinophilic obliterative bronchiolitis might be a cause of irreversible airflow obstruction in chronic eosinophilic respiratory diseases. Notably, whitish tracheal and bronchial granulations or bronchial ulcerative lesions can be present with prominent eosinophilia on bronchial biopsy [180].

Eosinophilic Lung Disease of Determined Cause

Once the diagnosis of eosinophilic pneumonia has been made, a thorough evaluation is necessary to investigate possible causes. A more comprehensive description of eosinophilic pneumonia related to fungi or parasites can be found elsewhere [188–190].

Eosinophilic Pneumonias of Parasitic Origin

The most common cause of eosinophilic pneumonia in the world, eosinophilic pneumonias related to parasite infestation arises mainly in humans infected by helminths and especially nematodes (roundworms).

Tropical Eosinophilia [191]

Tropical eosinophilia caused by the filarial nematodes *Wuchereria bancrofti* and *Brugia malayi* is endemic in tropical and subtropical areas of Asia, Pacific, Africa, and less commonly in South and Central America. It has been reported mostly in Indians, and occasionally in patients originating from India or Asia and living in western countries. It is characterized by severe spasmodic bronchitis or chronic dry cough (exacerbated at night), often associated with expiratory dyspnea and wheezing, fever, loss of weight, anorexia, leukocytosis, and high blood eosinophilia, and disseminated bilateral opacities at a chest X-ray. Eosinophilic pneumonia is generally seen 1–3 months after infestation. Blood eosinophilia is prominent, with more than 2×10^9 eosinophils/L in all cases, and up to 60×10^9/L in some cases. BAL shows intense alveolitis with a mean percentage of 54% of eosinophils with marked degranulation. Because the circulating microfilariae are trapped in the lung vasculature, they are usually not found in the blood or the lung. BAL eosinophils drop within 2 weeks upon anti-parasitic treatment. Lung function tests show a restrictive ventilatory defect, with a reversible obstructive ventilatory defect and hypoxemia in about a quarter of the patients. Nonspecific opacities are present on chest X-ray and CT in a majority of patients; irregular basilar opacities may persist for longer than 1 year. The diagnosis is made by the combination of cough worse at night; residence in a filarial endemic area; eosinophil count greater than 3300 cells/mm^3; and clinical and hematologic response to diethylcarbamazine. The latter is the only effective drug for tropical eosinophilia. Association of corticosteroids to diethylcarbamazine may be beneficial.

Ascaris Pneumonia

The most common helminth infecting humans, *Ascaris lumbricoides* is transmitted through food or water contaminated by human feces. Transient pulmonary infiltrates with blood eosinophilia (Löffler syndrome) may develop during the migration of the larvae of the parasite through the lung, with usually mild pulmonary symptoms (cough and wheezing), transient fever, a possible pruritic eruption at the time of respiratory symptoms. Blood eosinophilia may be as high as 22×10^9/L. Symptoms spontaneously resolve in a few days, whereas blood eosinophilia may remain elevated for several weeks. The diagnosis is made by the delayed finding of the worm or ovae in the stool within 3 months of the pulmonary manifestations. Intestinal ascariasis is treated with oral mebendazole.

Eosinophilic Pneumonia in *Larva Migrans* Syndrome

Visceral larva migrans is caused by *Toxocara canis*, and occurs mainly in children infected by eggs contaminating the soil of public playgrounds in urban areas. Whereas the majority of patients remain asymptomatic and undiagnosed, some present with fever, cough, dyspnea, seizures, fatigue, wheezes or crackles at pulmonary auscultation, and pulmonary opacities at a chest X-ray. Corticosteroids may be beneficial in rare severe cases in adults necessitating mechanical ventilation. Blood eosinophilia may be present initially, or may develop only in the following days. The diagnosis is difficult, as both IgG and IgM antibodies may reflect residual immunity rather than recent infection and do not have diagnostic significance [192]. Only symptomatic treatment is generally required. The use of anthelmintics is controversial. Corticosteroids seem beneficial in cases with severe pulmonary involvement.

Strongyloides Stercoralis Infection

Prevalent in the tropical and subtropical areas, infection with the intestinal nematode *Strongyloides stercoralis* is acquired through the skin by contact with the soil of beaches or mud and may persist for years, often without peripheral eosinophilia that is mostly present in recently infected patients [160, 193]. Löffler syndrome occurs when larvae migrate through the lungs after acute infection. Immunocompromised patients or those receiving immunosuppressive therapy are at risk of severe disseminated strongyloidiasis, which may affect all organs (hyperinfection syndrome). The diagnosis depends on the demonstration of larvae in the feces or sputum and BAL fluid. Immuno-diagnostic assays by ELISA methods may be useful for diagnosis and screening. All infected patients should be treated using ivermectin.

Eosinophilic Pneumonias in Other Infections

Löffler syndrome can also be caused by the human hookworms *Ancylostoma duodenale* and *Necator americanus*. Simple pulmonary eosinophilia may be due to cutaneous

helminthiasis (creeping eruption) related to the dog hookworm *Ancylostoma braziliense*. Transient multiple small pulmonary nodules at chest imaging and eosinophilia may occur in early acute schistosomiasis due to *Schistosoma haematobium* or *S. mansoni*, whereas post-treatment eosinophilic pneumonitis (also called reactionary Löffler-like pneumonitis) may develop in chronic schistosomiasis (in addition to the risk of portopulmonary hypertension) [194]. Other parasites causing rare pulmonary manifestations with eosinophilia include the filarial parasite of dog *Dirofilaria immitis* (the pulmonary fluke), *Paragonimus westermani*, *Trichomonas tenax*, *Capillaria aerophila*, and *Clonorchis sinensis*.

Pulmonary infection with eosinophilia has been reported occasionally with *Pneumocystis jirovecii*, fungi (*Coccidioides immitis*, *Bipolaris australiensis*, *Aspergillus niger* and *Bipolaris spicifera*), *bacteria* (tuberculosis, brucellosis), and viruses (respiratory syncytial virus, influenza infection).

Allergic Bronchopulmonary Aspergillosis

ABPA is a distinct condition characterized by asthma, eosinophilia, and bronchopulmonary manifestations with bronchiectasis due to the fungus *Aspergillus fumigatus*, and differing from invasive pulmonary aspergillosis, aspergilloma, *Aspergillus*-associated asthma, or chronic necrotizing aspergillosis, although it may be associated to the latter. ABPA is related to a complex allergic and immune reaction to *Aspergillus* colonizing the airways in susceptible hosts, namely 1–2% of adults with previous asthma and 7–10% [195, 196] of patients with cystic fibrosis. In addition, rare cases have been recently reported in patients with chronic obstructive pulmonary disease. Five stages have been described (acute, remission, recurrent exacerbations, corticosteroid-dependent asthma, and fibrotic end stage), although they do not reflect the natural course of disease in many patients, and alternative staging systems have been proposed [197]. Allergic *Aspergillus* sinusitis, a sinus equivalent of ABPA [198], can be associated with ABPA in a syndrome called *sinobronchial allergic aspergillosis*.

Pathogenesis

ABPA results from the persistence of *A. fumigatus* in the airways, and the skewing of adaptive immune responses to type 2 [199]. Damage to the bronchial epithelium, submucosa, and adjacent pulmonary parenchyma is caused by a chronic inflammatory reaction in the bronchi and the surrounding parenchyma. ABPA is mediated by type I and type III immunologic response of the host (mediated by IgE, and IgG and IgA antibodies, respectively), together with a Th2 $CD4^+$ T-cell mediated immune response and sustained IL-17 expression [200] to antigens from *Aspergillus* growing in mucous plugs in the airways. Cytolytic eosinophils release filamentous chromatin fibers and create extracellular traps, composed of condensed chromatin fibers and contribute to the high viscosity of eosinophilic mucus [201]. Eosinophils accumulated in the airways also release toxic cationic proteins [202], causing epithelial damage and leading to airways mucus plugging. The chronic inflammatory reaction, with the secretion of a variety of inflammatory cytokines and recruitment of inflammatory cells, results in damage to the bronchial epithelium, submucosa, and adjacent pulmonary parenchyma.

In addition to mechanisms associated with innate and acquired immunity, ABPA can occur preferentially in genetically susceptible hosts [197], as suggested by the increased prevalence of heterozygotic cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations [203, 204], and association with a polymorphism within the IL-4 receptor α-chain gene and HLA DR subtypes. Genetic susceptibility likely explains why not all patients with asthma develop ABPA despite the environment. Infection with nontuberculous mycobacteria [205], infliximab therapy for sarcoidosis [206], Kartagener syndrome, and occupational exposures (in workers in the bagasse-containing sites in sugar cane mills) [207] may also contribute to the pathogenesis of ABPA. In addition to *Aspergillosis*, other fungi or yeasts can cause a similar syndrome of allergic bronchopulmonary disease (reviewed in [208]), with difficulties in assessing the sensitization to the specific fungi probably accounting for part of the low frequency of recognition of these conditions as compared to ABPA.

Diagnostic Criteria

The diagnosis of ABPA is made on a combination of clinical, immunologic (microbiological), and thoracic imaging findings [199]. Several sets of criteria have recently been proposed (Table 17.10) [197, 209–211], as the diagnosis is generally made on the combination of clinical and biologic features. The classical diagnostic criteria include asthma, history of pulmonary infiltrates, proximal bronchiectasis, elevated serum IgE, and immunologic hypersensitivity to *A. fumigatus* (immediate reaction to prick test for *Aspergillus* antigen, precipitating antibodies against *A. fumigatus*, elevated specific IgE against *A. fumigatus* [209, 212]). The expectoration of mucous plugs, the presence of *Aspergillus* in sputum, and late skin reactivity to *Aspergillus* antigen [209] are also frequent findings that contribute to the diagnosis when present. Typical proximal bronchiectasis may be absent in cases designated ABPA-seropositive [213]. New diagnostic criteria consisting of ten components showed high sensitivity and specificity for the diagnosis of ABPA in patients without cystic fibrosis [211]; they are also useful for the diagnosis of allergic bronchopulmonary disease due to fungi other than *Aspergillus*.

Table 17.10 Diagnostic criteria of ABPA

Minimal essential diagnostic criteria of ABPA	
Rosenberg–Patterson criteria for diagnosis of ABPA in patients with asthma (1977) [209]	*Primary criteria*[a]
	1. Episodic bronchial obstruction (asthma)
	2. Peripheral blood eosinophilia
	3. Immediate skin reactivity to Aspergillus antigen
	4. Precipitating antibodies against Aspergillus antigen
	5. Elevated serum IgE concentrations
	6. History of pulmonary infiltrates (transient or fixed)
	7. Central bronchiectasis
	Secondary criteria
	• *A. fumigatus* in sputum (detected by repeated culture or microscopic examination)
	• History of expectoration of brown plugs or flecks
	• Arthus reactivity (late skin reactivity) to Aspergillus antigen
ISHAM criteria for diagnosis of ABPA (2013) [197]	Predisposing conditions: asthma, cystic fibrosis
	Obligatory
	• Positive type 1 *Aspergillus* skin test result or elevated IgE antibody levels
	• Total IgE level >1000 IU/mL
	And >2 of the following:
	• Precipitating or IgG serum antibodies to *A. fumigatus*
	• Radiographic pulmonary opacities consistent with ABPA
	• Eosinophil count >500 cells/mL in steroid-naive patients (may be historical)
Modified ISHAM criteria for diagnosis of ABPA in asthma (2020) [210]	Presence of the following:
	1. Asthma
	2. *A fumigatus*-specific IgE level >0.35 kU A/L
	3. Serum total IgE levels >500 IU/mL and >2 of the following:
	(a) *A fumigatus*-specific IgG level >27 mg A/L
	(b) Bronchiectasis on chest CT scan
	(c) Eosinophil count >500 cells/mL
	(d) Mucus impaction on chest CT scan
Asano criteria for diagnosis of ABPM in patients without cystic fibrosis (2021) [211]	Presence of >6 of the following:
	1. Current or previous history of asthma or asthmatic symptoms
	2. Peripheral eosinophilia >500 cells/mm^3
	3. Total IgE level >417 IU/mL
	4. Positive result of immediate skin test or specific IgE level for filamentous fungi[b]
	5. Presence of precipitins or specific IgE for filamentous fungi
	6. Positive filamentous fungal sputum test or bronchial lavage culture result
	7. Fungal hyphae in bronchial mucus plugs
	8. Central bronchiectasis on CT scan
	9. Mucus plugs detected by CT, bronchoscopy, or expectoration
	10. High-attenuation bronchial mucus on CT scan

ISHAM International Society of Animal and Human Mycology, *ABPM* allergic bronchopulmonary mycosis

[a]The diagnosis "likely" if primary criteria 1–6 are present and "certain" if all primary criteria are present

[b]Filamentous fungi in criteria 4–6 should be identical

Of note, patients who are negative for *Aspergillus fumigatus*-specific IgE are unlikely to have ABPA, a feature that is helpful to rule out the disease in severe asthmatics [197]. Similarly, a normal serum total IgE level excludes active ABPA disease [199]. The yield of sputum cultures for *A. fumigatus* is only about 40–60% in ABPA, therefore negative sputum cultures do not exclude ABPA [199]. However, since manifestations of ABPA are nonspecific, a high index of suspicion should be exerted in any asthmatic patient.

Biology

Pulmonary infiltrates with alveolar eosinophilia and/or peripheral blood eosinophilia may be present only during the acute phase or recurrent exacerbations of the disease. Blood eosinophilia is generally greater than 1×10^9/L. Sputum and expectorated plugs contain eosinophils and Charcot-Leyden crystals. Serum levels of TARC are elevated and might be used as a marker for the identification and monitoring of ABPA.

Demonstration of immediate and/or late immunologic hypersensitivity to *A. fumigatus* is key to the diagnosis of ABPA. Out of about 40 antigenic components of *Aspergillus* that can bind with IgE antibodies [213], two seem to be the most helpful for diagnostic purposes (e.g. specific antibodies to recombinant *rAsp f1* and *rAsp f2*) [199, 214–216].

Imaging

Proximal bronchiectasis on CT (in the medial half of the lung from the hilum to the chest wall) predominating in the upper lobes [217] is considered a hallmark of ABPA, albeit one with low sensitivity and specificity, and the finding may be absent especially in early disease [197]. It has been suggested that serological ABPA (without bronchiectasis) may correspond to a variant rather than an early stage of disease [218]. Bronchiectasis represents the ultimate consequence of damage to the large bronchi by chronic inflammation. Mucoid impaction of high attenuation on CT represents mucous plugs containing *Aspergillus* obstructing the airways with subsequent atelectasis [219]. Mosaic attenuation, centrilobular nodules, and tree-in-bud opacities are also commonly seen. The presence of bronchiectasis, centrilobular nodules, and mucoid impaction on CT scans are highly suggestive of ABPA in an asthmatic (Figs. 17.9, 17.10, and 17.11) [220]. Agarwal et al. have suggested a classification based on CT imaging patterns between serological ABPA (without bronchiectasis), ABPA with bronchiectasis, ABPA with high-attenuation mucus, and ABPA with pleuropulmonary fibrosis [197].

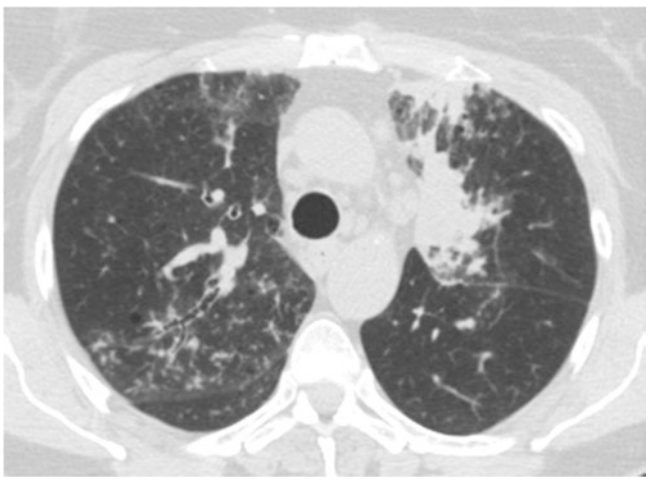

Fig. 17.9 CT scan of a patient with allergic bronchopulmonary aspergillosis showing central bronchiectasis and tree-in-bud pattern in the right upper lobe, with alveolar consolidation corresponding to eosinophilic pneumonia in the left upper lobe

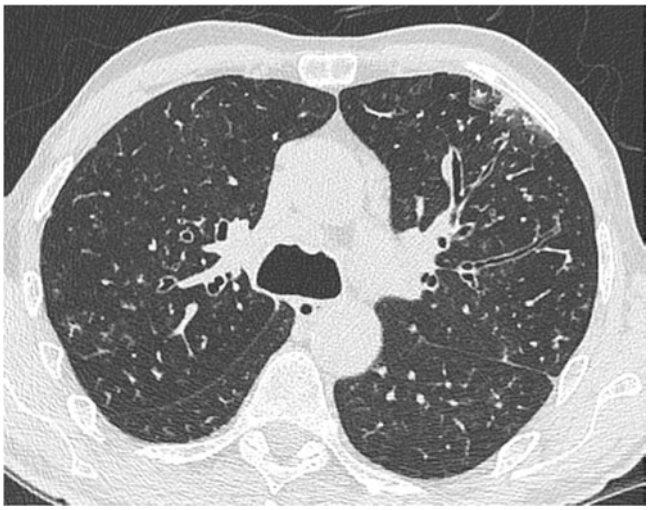

Fig. 17.10 CT scan of a patient with allergic bronchopulmonary aspergillosis showing central bronchiectasis predominating in the left upper lobe, with mild subpleural alveolar consolidation

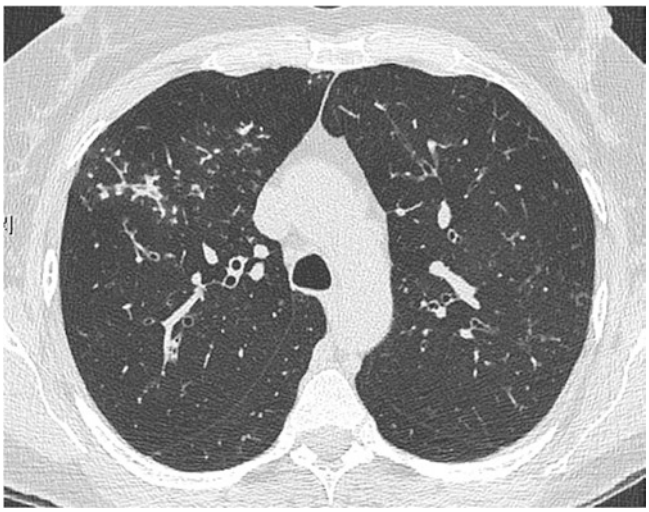

Fig. 17.11 CT scan of a patient with allergic bronchopulmonary aspergillosis showing peripheral tree-in-bud and branching pattern in the right upper lobe

On imaging, fleeting infiltrates due to eosinophilic pneumonia or mucus plugging with ensuing segmental or lobar atelectasis are frequent during the initial stage of the disease, however, the diagnosis is rarely made at this stage. A V-shaped lesion with the vertex pointing toward the hilum suggests mucoid bronchial impaction, which may be associated with atelectasis.

Treatment

Management of asthma is of primary importance in ABPA, often requiring high-dose inhaled corticosteroids (which may reduce the need for long-term oral corticosteroids) and long-acting bronchodilators. In addition, oral corticosteroids are used during acute exacerbations, with rapid tapering. Treatment is initiated at 0.5 mg/kg/day of prednisone for 1 or 2 weeks, then tapered over a total duration of about 12 weeks (short regimen) [213], a protocol which is now preferred to a longer regimen with higher doses of corticosteroids (0.75 mg/kg/day for 6 weeks, then tapered over a total duration of 6–12 months) [221–223]. Oral corticosteroids are maintained in the long-term only in patients with frequent symptomatic attacks or chronic symptoms, with the objective of preventing the progression to the fibrotic end stage, albeit with low-level evidence.

Antifungal therapy to attenuate the fungal load in the airways is an alternative to corticosteroids, or can be combined with corticosteroids [199]. Several randomized, placebo-controlled studies [224, 225] demonstrated that oral itraconazole allowed reduction of the doses of corticosteroids, a decrease in the number of exacerbations [225], and improvement of biologic (sputum eosinophils, sputum ECP levels, serum IgE levels, and serum IgG levels to *A. fumigatus*) and physiologic criteria. A clinical benefit accrued in approximatively 60% of patients with ABPA [226], especially those with corticosteroid-dependent ABPA, although no significant effect was observed on pulmonary infiltrates [227]. Itraconazole is therefore recommended in ABPA in asthmatics [228]. It can also be used as an alternative to oral corticosteroids [229]. Itraconazole may also be useful in ABPA patients with cystic fibrosis [226, 230]. Itraconazole therapy is generally continued for a minimum of 4–6 months. Monitoring total serum IgE level may be helpful, with the objective of reducing the serum total IgE level by ≥25% with therapy [197]. Itraconazole interacts with many medications, with a risk of adrenal insufficiency. Due to frequent drug interactions, the use of oral prednisone, and inhaled beclomethasone or ciclesonide, should be preferred to that of oral methylprednisolone and inhaled budesonide or fluticasone [226]. Voriconazole has been used in patients with acute-stage ABPA, however without proven benefit as compared to itraconazole [231].

In spite of total IgE levels that frequently exceed 1000 IU/mL, the anti-IgE recombinant antibody omalizumab may be useful in some cases to reduce the number of episodes of exacerbation and the steroid dose [232, 233], especially in subjects with treatment-refractory ABPA or those who are intolerant to first-line treatment [199]. In difficult cases, some clinical benefit was suggested with pulses of intravenous corticosteroids (to treat exacerbations), voriconazole, posaconazole, or nebulized liposomal amphotericin B [234]. More recently, mepolizumab, benralizumab, reslizumab, and dupilumab have been used successfully in isolated cases.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis [235] is a chronic inflammatory granulomatous and destructive process extending from the bronchiolar walls into the surrounding peribronchiolar lung parenchyma [236]. Pathology demonstrates destruction and necrosis of the mucosa and walls of bronchioles, often surrounded by palisading histiocytes and dense peribronchial inflammatory infiltrate, with occasionally scattered fungal hyphae stained by Grocott, and possible vascular inflammation and mucoid impaction [236]. In asthmatics, eosinophils are prominent within the inflammatory infiltrate of bronchocentric granulomatosis, whereas they are less conspicuous in nonasthmatics. Patients with bronchocentric granulomatosis often present clinically as asthmatics who have a fever, chronic cough, and peripheral blood eosinophilia greater than 1×10^9 eosinophils/L [236]. Imaging features consist of masses, alveolar opacities, consolidation, and possible reticulonodular opacities. Abnormalities all predominate in the upper lung zones and are generally unilateral [237]. Management is based on oral corticosteroids. As most of these patients also fulfill the criteria for ABPA, this condition may be underdiagnosed. Although the prognosis is excellent, recurrences are common.

Drug, Toxic Agents, and Radiation-Induced Eosinophilic Pneumonias

Eosinophilic pulmonary infiltrates can be caused by a number of drugs (Table 17.11, see www.pneumotox.com), with a demonstration of causality for only a few of them. The typical patient will present with acute (or chronic) onset of eosinophilic pneumonia following the recent initiation of treatment with nonsteroidal anti-inflammatory drugs or antibiotics. Simple pulmonary eosinophilia (Löffler syndrome with transient pulmonary infiltrates), or chronic eosinophilic pneumonia, can also be induced by drugs. Associated extrapulmonary iatrogenic manifestations, especially cutaneous rashes, fever, or nausea, may be present.

Table 17.11 Drugs that may commonly cause acute eosinophilic pneumonia. A more extensive list of drugs reported to cause eosinophilic pneumonia may be found at www.pneumotox.com

Anti-inflammatory drugs and related drugs	Acetylsalicylic acid, diclofenac, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, tolfenamic acid
Antibiotics	Ethambutol, fenbufen, minocycline, nitrofurantoin, penicillins, pyrimethamine, sulfamides, sulfonamides, trimethoprim-sulfamethoxazole
Other drugs	Captopril, carbamazepine, Granulocyte monocyte-colony stimulating factor (GM-CSF)

Pleural effusion is possible. Systemic eosinophilic vasculitis involving the lung and closely resembling EGPA has been reported. Cases with severe pulmonary involvement may require mechanical ventilation, or present with systemic manifestations (drug reaction with eosinophilia and systemic symptoms, DRESS) [238, 239]. Up to 75% of cases are associated with an antiviral immune response to reactivated human herpesvirus-6 [240].

A thorough history is required to suspect drug-induced eosinophilic lung disease, as the offending drug may have been taken in the weeks or months preceding the clinical syndrome, or may be denied by the patient as in the case of illicit drugs (cocaine, heroin, crack, marijuana/cannabis). Eosinophilic pneumonia can also be caused by non-cigarette smoking products including vaping, waterpipe smoking, and marijuana [241–243]. Pulmonary manifestations may regress after withdrawal of the suspected drug, confirming the diagnosis, however, this may take a long time, and therefore corticosteroids are also frequently given. Reintroduction of the suspected drug can be dangerous and should generally be avoided, although it may be carefully considered on rare occasions.

Historically, the toxic oil syndrome and the eosinophilia-myalgia syndrome related to preparations of L-tryptophan caused eosinophilic lung disease in Spain in 1981 and the United States in 1989, respectively.

A syndrome similar to ICEP can develop up to 10 months after radiotherapy for breast cancer in women [244]. Patients often have a history of asthma or allergy, presumably with a Th2-oriented lymphocyte response. Pulmonary opacities at imaging may be unilateral (irradiated lung) or bilateral, and occasionally migrate. Peripheral blood eosinophilia greater than 1.0×10^9/L and/or eosinophilia greater than 40% on the BAL differential cell count distinguish this syndrome from organizing pneumonia primed by radiation therapy to the breast. Rapid improvement is obtained with oral corticosteroids, with possible relapse after treatment withdrawal. Similar cases have also been reported following radiation therapy for lung cancer.

Miscellaneous Lung Diseases with Associated Eosinophilia

Eosinophilia in blood and/or in BAL has been found in several conditions not associated with typical eosinophilic pneumonia. For example, some overlap can occur between organizing pneumonia and ICEP, with BAL eosinophilia (that is typically moderate in organizing pneumonia), foci of organizing pneumonia in ICEP or conspicuous eosinophils in organizing pneumonia at pathology, or evolution of untreated CEP to organizing pneumonia.

The eosinophilic inflammation of the airways that is typical of asthma plays a direct role in disease pathogenesis [245] and correlates with the severity of the disease [246]. Asthma is frequent in eosinophilic lung diseases, especially ABPA, ICEP, and EGPA. BAL has shown mildly increased levels of eosinophils (usually <5%) on differential cell count in asthmatics. The eosinophilic phenotype of asthma, with eosinophilic airway inflammation and often little or no increase in the peripheral blood eosinophil counts, is a marker of steroid-responsive disease and elevated exacerbation risk and may respond to anti-IL5 monoclonal antibodies [247]. Patients with asthma and high-level blood hypereosinophilia (i.e., >1.0 and especially $>1.5 \times 10^{-9}$) or alveolar eosinophilia (>25% and especially >40%), are considered to have "hypereosinophilic asthma" [248, 249]. These patients frequently require high-dose inhaled or even oral corticosteroids and should be monitored closely as they may progress to EGPA, ABPA, hypereosinophilic obliterative bronchiolitis, or ICEP.

Eosinophilic bronchitis (without asthma) is defined by a high percentage of eosinophils in the sputum with normal lung function and absence of bronchial hyperreactivity [250]; eosinophilic bronchitis is clearly distinct from asthma and from hypereosinophilic obliterative bronchiolitis, however it can cause chronic cough responsive to inhaled corticosteroid treatment [251], and rarely may evolve to irreversible airflow obstruction [252, 253]. Treatment with an antagonist of the eotaxin tissue receptor CCR3, the receptor for eotaxin and other chemokines, may be beneficial [254]. Eosinophilic bronchitis is distinct from bronchial asthma, although it may in rare cases.

Mildly increased levels of eosinophils may be found at BAL differential cell count or may be focally present histopathologically in the idiopathic interstitial pneumonias. In pulmonary Langerhans cell histiocytosis, the pathologic lesions consist of nodules with a bronchiolocentric stellate shape composed of Langerhans cells with variable numbers of eosinophils, especially in the initial active stage and at the periphery of the lesions. Eosinophilic alveolitis in lung transplant recipients may be indicative of acute rejection (tissue eosinophilia is involved in rejection after renal, cardiac, hepatic, and pancreatic transplantation). BAL eosinophilia of 2% or greater is associated with a poor outcome in lung transplantation [255], or may result from infection.

Clinical Vignette

A 32-year-old female, never-smoker, with an 8-year history of chronic rhinosinusitis with nasal polyposis and asthma for the last 4 years, was admitted for acute onset of dyspnea and skin manifestations. She had no history of allergic manifestations. The severity of asthma had increased over the past year, and montelukast had been prescribed 4 months ago by her general physician in addition to her long-term treatment with inhaled long-acting corticosteroids and bronchodilators. On admission, she presented with acute exacerbation of asthma, nasal obstruction with nasal crusts, asthenia, arthralgia, palpable purpura of the lower extremities, and neuropathy consistent with mononeuritis multiplex. The chest radiograph showed areas of ground glass opacity, with patchy peripheral bilateral alveolar consolidation on chest CT. The peripheral blood eosinophil count was 5.6×10^9/L. The differential cell count of bronchoalveolar lavage demonstrated 65% eosinophils, 4% neutrophils, 7% lymphocytes, and 24% macrophages. Skin biopsy showed leukocytoclastic vasculitis. Antineutrophil cytoplasmic antibodies were negative. Electrocardiogram, echocardiography, and serum troponine level were normal. Pulmonary function tests showed airflow obstruction, with marginal improvement with inhaled bronchodilators. The patient was diagnosed with eosinophilic granulomatosis with polyangiitis and was treated with oral prednisolone (1 mg/kg/day for 1 month then progressively tapered). Montelukast was discontinued. Complete remission was obtained. Three years later, the patient now complains of chronic rhinosinusitis, dyspnea on exertion with nonreversible moderate airflow obstruction despite high-dose inhaled anti-asthmatic therapy and 5 mg/day of oral prednisolone. There are no apparent systemic sequelae of her vasculitis. Peripheral blood eosinophils are 0.6×10^9/L despite oral prednisolone. Benralizumab is initiated, allowing rapid discontinuation of prednisolone and improvement in lung function tests.

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