

Review article

Eosinophilic pneumonias

Eosinophilic pneumonias (EP) encompass a wide spectrum of lung diseases characterized by peripheral blood eosinophilia ($> 1 \times 10^9$ eosinophils/l) and/or alveolar eosinophilia ($> 25\%$). Blood eosinophilia may be lacking, as in the early phase of idiopathic acute EP, or in patients already taking oral corticosteroids. EP may present with varying severity, ranging from almost asymptomatic infiltrates to the acute respiratory distress syndrome necessitating mechanical ventilation. Possible causes of EP must be thoroughly investigated, especially drugs and the variety of parasitic infections (considering history of travel or residence in areas of endemic parasitic infection). However, chronic EP remains idiopathic in many cases. When present, extrathoracic manifestations lead to suspect Churg–Strauss syndrome (CSS) or the hypereosinophilic syndrome (HES), the prognosis of which is dominated by cardiac involvement. Apart from the treatment of specific causes when possible, corticosteroids remain the cornerstone of symptomatic treatment for eosinophilic disorders, usually with a dramatic response, but frequent relapses when tapering or after stopping the treatment. The adjunction of immunosuppressants to corticosteroids is necessary in patients with CSS and poor prognosis factors. Imatinib has recently proven effective in the treatment of the myeloproliferative variant of the HES.

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The group of eosinophilic pneumonias (EP) encompasses a variety of infiltrative lung diseases characterized by prominent infiltration of the lung parenchyma by eosinophils, cells believed to exert a causative role in the lesional process (1, 2). Because of its very characteristic morphology and staining properties, the eosinophil is easy to detect in tissues and biological fluids. Peripheral blood eosinophilia (more than $1.0 \times 10^9/l$ and especially $1.5 \times 10^9/l$) is usual in EP but not constant. Distinct clinical and radiological patterns, as well as the aetiologic context have led to the characterization of several well-defined entities, including EP of undetermined cause [idiopathic chronic and acute EP, Churg–Strauss syndrome (CSS), and the hypereosinophilic syndromes (HES)]; EP of determined cause such as EP secondary to parasitic infections, drug- or radiation-induced reactions, and allergic bronchopulmonary aspergillosis (ABPA); and a miscellaneous group of lung diseases where some degree of eosinophilia may be encountered. A characteristic and original feature of EP is the dramatic response to corticosteroids, with a favourable outcome without any sequelae in most of the cases, even in patients with an acute and severe or life-threatening presentation. Eosinophils dramatically disappear from the bloodstream within a few hours after administration of corticosteroids (3), as a result of their sequestration in tissues and cell death mainly by apoptosis. As a consequence, EP may be missed when

corticosteroids have been taken before a differential blood cell count was carried out. Adequate initial management is mandatory to rapidly establish the diagnosis of EP, most of the time through noninvasive procedures.

The eosinophil leukocyte

As infiltration of the lung by eosinophils is a hallmark of EP, particular attention has been paid to the biopathology of this cell type (4–7). The eosinophil has a potent array of secretory products involved in the nonspecific inflammatory response and protection against infectious organisms, and may participate to tissue injury in eosinophilic disorders. The eosinophil is also considered an actor of the immunological response within the lung, with many biological properties of eosinophils directed by T-helper lymphocytes, as well as interaction with other cell types such as mast cells and basophils, endothelial cells, macrophages, platelets and fibroblasts. The diversity of mediators released by the eosinophil under various conditions, and/or surface enzymes, receptors for cytokines, chemokines, complement proteins and other chemotactants suggests that this cell type is involved in a variety of allergic and/or inflammatory processes.

Bone marrow-derived eosinophil precursors differentiate in 5 days under the action of several cytokines

including interleukin (IL)-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (8), into mature eosinophils (12–15 μm in diameter) which then circulate within the blood for about 1 day before being recruited into target tissues such as the lung. Recruitment of eosinophils is a complex and dynamic process involving cell adhesion and attraction, diapedesis, and chemotaxis by cytokines such as IL-5 and eotaxin. Once in tissues, eosinophils undergo rapid apoptosis unless survival factors are present. The main biological effects of mature eosinophils are thought to occur in tissues, where they may release active mediators upon activation, including proinflammatory cytokines, arachidonic acid-derived mediators, enzymes and reactive oxygen species. In addition, the release of toxic substances by activated eosinophils may in itself contribute to the pathophysiology of eosinophilic disorders. In particular, the eosinophil contains small and amorphous intracytoplasmic granules rich in arylsulphatase and acid phosphatase, and larger intracytoplasmic granules characterized by an electron-dense crystalloid matrix containing the characteristic cationic proteins. Activation and degranulation of the eosinophil results in the extracellular release of the eosinophil specific proteins including major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) also called eosinophil-protein X (EPX), enzymatic protein eosinophil peroxidase (EPO) and the more recently described MBP homologue. Degranulated eosinophils may be recognized in tissue sections by their vacuolated cytoplasm on microscopy, as well as their characteristic ultrastructural appearance on electron microscopy with the lack of the electron-dense central core of the granules. The eosinophils also express major histocompatibility complex class II molecules and costimulatory molecules, and may function as antigen-presenting cells to promote expansion of sensitized CD4⁺ Th2 lymphocytes (9, 10).

The physiological role of the eosinophil still remains unclear. Mice with a complete and selective loss of the eosinophil lineage [generated by gene targeting of the transcription factor GATA-1 (11) or through transgenic expression of the diphtheria toxin A chain under the control of the EPO promoter (12)] develop normally and appear healthy. Studies in such eosinophil-deficient mice will undoubtedly lead to new insights into the part played by eosinophils in the pathogenesis of eosinophil-related disorders. For example, such eosinophil-deficient mice were protected from airway remodelling but not allergen-induced airway dysfunction in an animal model of asthma (13). The eosinophil is involved in many inflammatory processes occurring in a variety of organs, especially the airways and the lung, where its role may be either beneficial or detrimental. For example, an eosinophil-mediated inflammatory response is usually considered beneficial during parasitic infestation, whereas eosinophilic infiltration of the bronchial wall participates to the pathophysiology of asthma. Although major advances have been made in the understanding of eosinophil biology, it

remains to be determined how the different stimuli potentially induce the differential release of the variety of granule proteins and/or cytokines contained and/or synthesized by this cell type. Of note, research on eosinophil is hampered by the inability of murine eosinophils to degranulate either *in vivo* or *in vitro*, in contrast with human eosinophils, and observations issued from animal studies may not always be applicable to human disease.

Hopefully, progress made in the understanding of the pathobiology of eosinophil leucocytes may lead to the discovery of new drugs targeting the recruitment or the activation of eosinophils, or inducing the apoptosis of this cell type (14). Hence, drugs that affect eosinophil development are becoming available (15), such as anti-IL-5 antibodies [which induce bone marrow eosinophil maturation arrest and decrease eosinophil progenitors in the airways (16)] or CCR3 antagonists [which might suppress eosinophil progenitor migration and maturation (17)]. Recent strategies targeting IL-5 have shown poorly effective in asthma, probably because eosinophil recruitment to the lung and activation results from redundant cytokine and signalling pathways (for example IL-5 and eotaxin) (14, 18), but more promising results have been obtained in the HES (19). Eosinophils also express potential inhibitory receptors that may provide novel therapeutic approaches (20).

Pathology

EP are characterized by the prominent infiltration of the lung parenchyma by eosinophils on histopathological examination, while other inflammatory cells may be associated, especially lymphocytes, plasma cells and polymorphonuclear neutrophils. The pathological features described in idiopathic chronic EP (ICEP) may be considered as the common denominator of all categories of EP (21–23), and may further be in some cases associated with features specific for the cause of EP. Alveolar spaces are also filled with eosinophils (that may be degranulated) (24) and a fibrinous exudate, with conservation of the global architecture of the lung. Eosinophilic microabscesses and a non-necrotizing vasculitis are common in ICEP and especially in idiopathic acute EP (IAEP) (25). Macrophages and scattered multinucleated giant cells may be present in the infiltrate and may contain eosinophilic granules or Charcot–Leyden crystals. Some degree of organization of the alveolar exudate is common, yet intraluminal organization of the distal airspaces is never prominent (in contrast with cryptogenic organizing pneumonia).

Diagnosis

The diagnosis of EP requires both characteristic clinical–radiological features and the demonstration of alveolar

(and/or peripheral blood) eosinophilia. Bronchoalveolar lavage (BAL) has become a widely accepted noninvasive surrogate of lung biopsy for the diagnosis of EP. Therefore, lung biopsy is seldom necessary to establish the diagnosis of EP, and is now performed only in difficult cases, where a video-assisted thoracoscopic lung biopsy should be preferred to transbronchial lung biopsies. The clinical–radiological presentation distinguishes three distinct presentations, namely Löffler syndrome, chronic EP and acute EP. In most cases the diagnosis of EP is made when both radiographic pulmonary opacities and alveolar eosinophilia are present, although no study has definitely established that an increased differential cell count of eosinophils at BAL unequivocally predicts a pathological finding of EP on lung biopsy. Although the percentage of eosinophils at BAL is <2% in normal controls (26), a differential cell count of eosinophils of 2–25% may be found in nonspecific conditions; therefore a cut-off of ≥25% for the diagnosis of IAEP has been recommended (27), and ≥40% for the diagnosis of ICEP (28, 29). In addition, the diagnosis of EP is supported by alveolar eosinophilia when the eosinophils are the predominant cell population of BAL differential cell count (macrophages excepted). The presence of markedly elevated peripheral blood eosinophilia ($>1 \times 10^9/l$ and preferably $1.5 \times 10^9/l$) together with typical clinical–radiological features obviates the need for lung biopsy in ICEP. However, peripheral blood eosinophilia may be absent at presentation especially in IAEP.

In clinical practice the EP may be separated into idiopathic EP, that usually may be included within well-individualized syndromes (ICEP, IAEP, CSS and the HES), and EP with a definite cause on the other hand, mainly of infectious and drug origin (Table 1). Identification of a cause may lead to therapeutic measures such as stopping a drug responsible for iatrogenic EP or treating a parasitic infection, and potential causes must be thoroughly investigated.

Idiopathic chronic eosinophilic pneumonia

Either chronic or acute, idiopathic EP represents an eosinophilic pulmonary disorder without associated manifestations specific for any aetiological agent. Individualized as a distinct entity by Carrington et al. (21), ICEP is characterized by the progressive onset of respiratory and systemic symptoms within a few weeks, with a mean interval of 4 months between the onset of symptoms and the diagnosis (29). The most common symptoms are cough, dyspnoea and chest pain (23, 29), often accompanied with fatigue, malaise, fever and weight loss. Haemoptysis and pleural effusion are uncommon. At physical examination, wheezes or crackles are found in one-third of patients. Chronic rhinitis or sinusitis is present in 20% of patients.

A majority of patients with ICEP (93.5%) were nonsmokers in our series (29), suggesting that smoking

Table 1. Classification of the eosinophilic lung diseases

Eosinophilic lung disease of undetermined cause
Solitary
Idiopathic chronic eosinophilic pneumonia
Idiopathic acute eosinophilic pneumonia
Associated with systemic disease
Churg–Strauss syndrome
Hypereosinophilic syndromes
Eosinophilic lung disease of determined cause
Eosinophilic pneumonias of parasitic origin
Tropical eosinophilia
<i>Ascaris</i> pneumonia
Larva migrans syndrome
<i>Strongyloides stercoralis</i> 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
Toxic agents
Eosinophilic pneumonia induced by radiation therapy to the breast
Miscellaneous lung diseases with possible associated eosinophilia
Organizing pneumonia
Asthma and eosinophilic bronchitis
Idiopathic interstitial pneumonias
Langerhans cell granulomatosis
Lung transplantation
Other lung diseases with occasional eosinophilia
Sarcoidosis
Paraneoplastic eosinophilic pneumonia

might be protective. ICEP occurs predominantly in women with a 2 : 1 female to male ratio, with a mean age of 45 years at diagnosis, and a prior history of atopy in about half of the patients. Prior asthma may be present in up to two-thirds of the patients, and may get worse after the occurrence of ICEP, requiring long-term oral corticosteroid treatment. Asthma may also occur concomitantly with the diagnosis of ICEP or develop after it (28). The presentation of ICEP is similar in asthmatics and non-asthmatics. There is no evidence that a desensitization programme may contribute to the development of ICEP.

Imaging features of ICEP consist of peripheral alveolar opacities present in almost all cases, with ill-defined margins and a density varying from ground glass to consolidation (Fig. 1). Migration of the infiltrates is highly suggestive of the diagnosis (although it may also be seen in cryptogenic organizing pneumonia) but is present in only a quarter of the cases (29). The peripheral predominance of the lesions described as the classic pattern of ‘photographic negative of pulmonary oedema’, very evocative of ICEP (30), is seen in only one-fourth of patients (23). Corticosteroid treatment is followed by a dramatic disappearance of pulmonary opacities. On high-resolution computed tomography (HRCT), the opacities are almost always bilateral and predominate in the upper

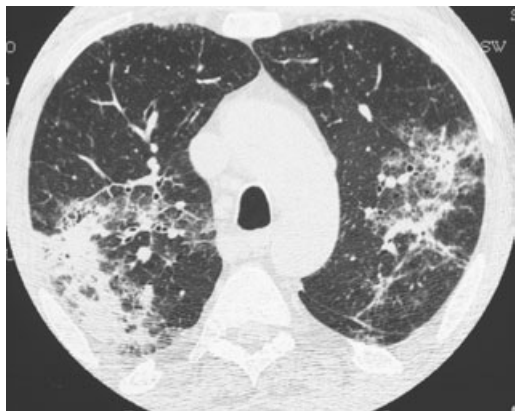


Figure 1. High-resolution computed tomography in a patient with idiopathic chronic eosinophilic pneumonia, showing predominantly peripheral alveolar opacities as well as ground glass opacities.

lobes. The most common features at HRCT are coexisting peripheral ground glass and consolidation opacities (29, 31, 32). In addition, septal line thickening, band-like opacities parallel to the chest, segmental or lobar atelectasis, small pleural effusions or mediastinal lymph node enlargement may be seen.

Peripheral blood eosinophilia is usually high and thus contributes to the diagnosis: eosinophilia over 6% was present in 88% of 111 cases in the literature (23). The mean blood eosinophilia was $5.5 \times 10^9/l$ in our series (29), with eosinophils representing a mean of 32% of the total blood leucocyte count. As peripheral blood eosinophilia is often a diagnostic criterion of ICEP, the proportion of patients with normal peripheral blood count is not accurately known. C-reactive protein and erythrocyte sedimentation rate are elevated. Total blood IgE level is increased in about half of cases (29). Circulating immune complexes and occasionally antinuclear antibodies may be present. Markedly increased urinary EDN level indicating active eosinophil degranulation is found in patients with ICEP (33).

A particularly marked alveolar eosinophilia usually >40% (with a mean of 58% in our series) at BAL differential cell count is a hallmark of ICEP (29). An increased percentage of neutrophils, mast cells and/or lymphocytes (mainly of the memory T cells with a CD4+ CD45RO+, CD45RA-, CD62L- surface antigen phenotype) may also be found. The BAL eosinophil cell count rapidly drops upon corticosteroid treatment. BAL eosinophils of patients with ICEP release eosinophil proteins and show a degranulated pattern on electron microscopy (34). They show increased surface expression of CD44, an adhesion molecule that participates in cell recruitment, while soluble CD44 is also increased in BAL fluid (35). Activation of eosinophils may be restricted to tissue eosinophils, as expression of the human leucocyte antigen (HLA)-DR was present in 86% of alveolar eosinophils in

contrast to only 7% of blood eosinophils in a patient with ICEP (36). Eosinophil apoptosis mediated by Fas may be suppressed in BAL eosinophils (37). EDN, ECP and immunoglobulins are increased in the BAL of patients with ICEP (1), as well as the eosinophil chemokines RANTES, eotaxin, and thymus- and activation-regulated chemokine (TARC/CCL17) (38–40), and the Th2 cytokine IL-3, IL-5, IL-13 and IL-18 (40, 41).

Nonrespiratory manifestations are uncommon in ICEP, although ICEP may be a presenting feature of – or overlap with – CSS (42, 43). Arthralgias, ST-T abnormalities on the electrocardiogram, acute pericarditis, elevated liver blood tests, mononeuritis multiplex, skin nodules or vasculitis, and diarrhoea or abdominal pain due to eosinophilic enteritis have been occasionally reported (21, 29, 44). Such patients with nonrespiratory manifestations are often treated with corticosteroid treatment, which may prevent the development of overt systemic vasculitis (44).

Lung function tests in ICEP show an obstructive ventilatory defect in about half the patients (23, 29) and a restrictive ventilatory defect in half the cases (29). PaO₂ 10 kPa or less is present in two-thirds of the patients, and CO transfer factor <80% of predicted is found in half the cases. Treatment is usually followed by the rapid normalization of lung function tests, with the exception of some patients in whom a ventilatory obstructive defect may persist (45).

As ICEP responds dramatically to corticosteroids, the natural course of the untreated disease is not well known. Spontaneous resolution has been reported. Corticosteroids are the mainstay of the treatment, with usual doses between 20 and 60 mg/day of prednisone. We recommend an initial dose of 0.5 mg/kg/day for 2 weeks, followed by 0.25 mg/kg/day for 2 weeks, then 10 mg/day for 2 weeks, and the corticosteroid treatment is stopped. Improvement of the symptoms occurs within 2 weeks (even within 48 h in about 80% of cases), and chest X-ray opacities clear within 1 week in about 70% of patients, and disappear eventually in almost all patients (29). Due to a high rate of relapse (>50%) while decreasing or after stopping the corticosteroid treatment, most patients receive corticosteroids for more than 6 months, and often several years. Relapses may occur in the same areas or in different areas of the lungs and respond very well on resumption of corticosteroid treatment. It has been suggested that relapses of ICEP may be less frequent in patients who receive inhaled corticosteroids after stopping maintenance oral corticosteroids (28, 29), but this is controversial (46).

Idiopathic acute eosinophilic pneumonia

IAEP (25, 27, 47–51) differs from ICEP by its acute onset and severity, and the absence of relapse after recovery. It presents as an acute pneumonia in previously healthy

individuals, with possible respiratory failure fitting the criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). In addition, blood eosinophilia is often lacking at presentation and contrasts with frank alveolar eosinophilia at BAL.

IAEP occurs at a mean age of about 30 years, ranging from < 20 to 86 years (27, 51). In contrast with ICEP, a male predominance but no prior asthma history are found (47). Particular attention must be paid to potential respiratory exposures, as patients have been reported to have had a variety of activities within the days before onset of disease, such as cave exploration, plant repotting, wood pile moving, smoke-house cleaning, motocross racing in dusty conditions, indoor renovation work, tank cleaning and explosion of a tear gas bomb (27, 51). Another case of IAEP has been reported in a New York City fire-fighter exposed to World Trade Center dust (52). In addition, in several cases IAEP has developed soon after the initiation of tobacco smoking (53–57), sometimes with a positive rechallenge test with cigarette smoking. It is likely that inhalation of smoke or any nonspecific injurious agent may at least contribute to the initiation or development of the disease.

The clinical presentation of IAEP is nonspecific, with the acute onset of cough, dyspnoea, fever and chest pain, sometimes associated with abdominal complaints or myalgias (27). Physical examination reveals tachypnoea, tachycardia, and crackles or less often wheezes on auscultation. Chest X-ray shows bilateral infiltrates, with mixed alveolar or interstitial opacities (27, 49–51). Chest CT mainly shows ground glass opacities and airspace consolidation, together with poorly defined nodules and interlobular septal thickening. A bilateral pleural effusion is present in at least two-thirds of patients (27, 49, 51, 58). The chest X-ray returns to normal within 3 weeks.

Contrasting with the usual lack of blood eosinophilia at presentation, the BAL differential cell count of eosinophils is usually >25% [with a mean of 37% (27) to 54% (51)], a finding that may be considered a diagnostic feature of the disease, obviating the need of a lung biopsy. Increased levels of eotaxin and GM-CSF and especially IL-5 have been reported in the BAL fluid of patients with IAEP (34, 59). The peripheral blood eosinophil count may rise to high values during the course of disease, a time course suggestive of the diagnosis (27, 47, 51). Eosinophilia may be also found in pleural effusion or sputum. High levels of IgE may be present. Lung function tests may show a mild restrictive ventilatory defect, a reduced transfer factor (60), and increased alveolar–arterial oxygen gradient (27). Severe hypoxemia may be present (48–51), with a majority of patients fulfilling diagnostic criteria of ALI (including a $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg) or of the ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg), so that mechanical ventilation is necessary in most of them (27, 51), but extrapulmonary organ failure is very rare. Lung function tests return to normal in most patients.

Lung biopsy shows acute and organizing diffuse alveolar damage together with interstitial alveolar and bronchiolar infiltration by eosinophils, intraalveolar eosinophils and interstitial oedema (25, 61). Although recovery without corticosteroid treatment may occur (51), a corticosteroid treatment is usually given for 2–4 weeks whenever a diagnosis of IAEP is made (27). Complete clinical and radiological recovery occurs rapidly upon corticosteroid treatment, with no relapse, in contrast with ICEP.

Diagnostic criteria previously proposed for IAEP (27) include an acute onset, with up to 7 days between the first symptoms and presentation. However, a further study in 22 patients showed no significant difference between patients seen between 7 and 31 days after the first symptoms and patients with a shorter onset in terms of their clinical presentation, BAL differential cell count, severity of respiratory failure and outcome (51). Therefore, diagnostic criteria of IAEP may be extended to patients presenting up to 1 month after the onset of the first symptoms, and we propose modified diagnostic criteria of IAEP (Table 2). Notably, response to corticosteroid therapy is not a reliable diagnostic criterion of IAEP as patients may recover spontaneously without steroids (47, 51).

Churg–Strauss syndrome

Described in 1951 by Churg and Strauss in autopsied cases (62), the eponymous syndrome has been included in the group of small vessel vasculitides in the Chapel Hill Consensus Conference (63). It is defined as an eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium sized vessels, and associated with asthma and eosinophilia. The pathological lesions of CSS (64, 65) include a vasculitis of the medium-sized pulmonary arteries (necrotizing or not), eosinophilic tissue infiltration, and extravascular granulomas consisting of palisading histiocytes and giant cells. However, all of these features are seldom found on a single biopsy, and lesions currently observed are often limited to an eosinophilic

Table 2. Diagnostic criteria for idiopathic acute eosinophilic pneumonia

1. Acute onset of febrile respiratory manifestations (≤ 1 month, and especially ≤ 7 days duration before medical examination)
2. Bilateral diffuse infiltrates on chest radiograph
3. PaO_2 on room air ≤ 60 mmHg (7.9 kPa), or $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg (40 kPa), 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 determined cause of acute eosinophilic pneumonia (including infection or exposure to drugs known to induce pulmonary eosinophilia, see Table 5)

Recent onset of tobacco smoking or exposure to inhaled dusts may be present

(perivascular) infiltration of the tissues characteristic of the early (prevasculitic) phase of the disease. Biopsy of the cutaneous lesions is the most common and simple procedure to obtain pathological evidence of vasculitis.

The clinical features of CSS have been well defined (66–71). CSS is a very rare vasculitis occurring especially in the fourth and fifth decades (70), with no sex predominance. A history of allergic rhinitis is present in three quarters of cases, often accompanied by relapsing paranasal sinusitis, polyps, and crusty rhinitis that does not lead to nasal septal perforation or deformation. Asthma, generally severe and becoming rapidly corticoid-dependent, usually precedes the onset of vasculitis by 3–9 years (66, 70, 72, 73), although this interval may be much longer (73), or asthma and vasculitis may be contemporary (72). The severity of asthma may attenuate with the onset of the vasculitis. The chest X-ray may remain normal throughout the course of the disease. Present in 37–72% of the cases (66, 70), lung opacities mainly consist of ill-defined pulmonary infiltrates, sometimes migratory, transient and of varying density (70, 73–75). A mild pleural effusion may be observed. In contrast to Wegener granulomatosis, pulmonary cavitary lesions are exceptional. HR-CT mainly shows areas of ground-glass attenuation or airspace consolidation, with peripheral predominance or random distribution, and less commonly centrilobular nodules, bronchial wall thickening or dilatation, interlobular septal thickening, hilar or mediastinal lymphadenopathy, pleural effusion and pericardial effusion (58, 75, 76). These abnormalities are nonspecific and allowed a correct diagnosis of CSS on CT in fewer than half the patients with eosinophilic lung diseases (58).

Blood eosinophilia often $> 5 \times 10^9/l$ usually parallels the vasculitis activity (66, 70, 73) and disappears dramatically after the initiation of corticosteroid treatment. Eosinophilia, sometimes $> 60\%$, is also found on BAL differential cell count (77). Anti-neutrophil cytoplasmic antibodies (ANCA) are common, reported in 48% (66) to 73% (72) patients, and contribute to the diagnosis. ANCA are mainly perinuclear-ANCA (P-ANCA) with myeloperoxidase specificity (66, 72). IgE levels are usually markedly increased. High levels of urinary EDN might represent an indicator of disease activity (78). T-cell lines derived from the blood of patients with CSS produce large amounts of Th2 cytokines such as IL-4 and IL-13, as well as interferon- γ (59). Serum IL-5 may be elevated (79, 80). Serum levels of IL-10 are elevated, while serum levels of IL-4, IL-5, IL-13 and interferon- γ were comparable with those found in Wegener's granulomatosis in another study (81).

Extrapulmonary manifestations of CSS usually include asthenia, weight loss, fever, arthralgias and/or myalgias (82). Neurological involvement mainly consists of mononeuritis multiplex, present in 77% of patients (66), or asymmetrical polyneuropathy, while central nervous system involvement is less common. Cardiac involvement

with eosinophilic myocarditis and/or coronary arteritis (66, 70–73) is often insidious and asymptomatic, and thus may be underrecognized. It may lead to dilated cardiomyopathy and require heart transplantation when left untreated, although eosinophilic myocarditis may markedly improve with corticosteroid treatment. Pericardial effusion is common in CSS but tamponade is rare. Endomyocardial involvement is not a common feature. Digestive tract involvement present in 31% of cases (66) usually manifests as isolated abdominal pain or diarrhoea, but intestinal vasculitis (with ulcerations, perforations, or haemorrhage of the oesophagus, stomach or intestine) and vasculitic cholecystitis may be present. Cutaneous lesions present in about half of patients (66) mainly consist of palpable purpura of the extremities, subcutaneous nodules, erythematous rashes and urticaria. Renal involvement present in a quarter of cases is usually mild (66).

The evolution of CSS typically follows three stages: asthma and rhinitis; tissue eosinophilia (such as EP); and extrapulmonary manifestations with vasculitis. As many patients receive corticosteroids at an early stage of the disease for asthma, the diagnosis of CSS is often delayed in patients with a mild presentation of the disease (the so-called 'formes frustes' of CSS). Such patients may later develop an overt presentation of the vasculitis especially when treatment is tapered. Thus the diagnosis of CSS should be considered and established before severe organ involvement (especially cardiac) is present.

There are currently no established or consensus diagnostic criteria for CSS. Lanham et al. (70) have proposed three diagnostic criteria including 1) asthma; 2) eosinophilia exceeding $1.5 \times 10^9/l$; and 3) systemic vasculitis of two or more extrapulmonary organs. Classification criteria (which are not *diagnostic* criteria however) of the American College of Rheumatology (83) may also be used in patients with a pathologically proven diagnosis of vasculitis. ANCA should probably be considered a major diagnostic criterion when present. A pathological diagnosis of CSS may be obtained from skin, nerve, or muscle biopsies, but this is not mandatory in most cases (66). Lung biopsy and transbronchial biopsies are not recommended.

CSS may occasionally be difficult to distinguish from the other ANCA-associated vasculitides especially the eosinophilic variant of Wegener granulomatosis (84). Cases of 'limited' CSS (85) involving only the lung or the heart and 'formes frustes' of CSS may be similar to other eosinophilic syndromes, such as ICEP or idiopathic HES with minor extrathoracic symptoms.

Corticosteroids are the mainstay of treatment of CSS (70, 86, 87), with an initial methylprednisolone bolus in the most severe cases, then oral treatment usually started at 1 mg/kg/day of prednisone and prolonged for several months with progressive tapering. About half the patients without poor prognostic factors at onset achieve complete remission with corticosteroid treatment alone and

do not relapse (88). Relapses of the vasculitis are common, and should be distinguished from the relapse or persistence of simple asthma (with generally $<0.5 \times 10^9/l$ blood eosinophils). Immunosuppressive treatment (such as azathioprine or pulses of cyclophosphamide) in addition to corticosteroids increase the risk of infections and are reserved to a minority of patients with manifestations that could result in mortality or severe morbidity (89), to patients with poor prognostic factors at onset (proteinuria >1 g/day; renal insufficiency with serum creatinine >15.8 mg/l; gastrointestinal tract involvement; cardiomyopathy; central nervous system involvement) (86), and to those with mild or severe relapses. Treatment with cytotoxic agents does not efficiently prevent relapses (90). Subcutaneous interferon- α has been successfully used in CSS patients with severe disease (91). The prognosis of CSS has considerably improved over the years with 79% of patients alive at 5 years (86).

CSS is considered as an autoimmune process involving T cells, endothelial cells and eosinophils (82). The possible role of allergy has been suspected especially in cases with allergic rhinitis and a family history of atopy. The possible role of triggering or adjuvant factors such as vaccines or desensitization has been suspected (92). In addition, the role of *Aspergillus*, allergic bronchopulmonary candidiasis, *Ascaris*, bird exposure or cocaine has been discussed in isolated case reports (82). Drug-induced eosinophilic vasculitis with pulmonary involvement has been formerly reported with sulphonamides (used together with antiserum), and with diflunisal, macrolides and diphenylhydantoin (1). The possible responsibility of leucotriene-receptor antagonists (montelukast, zafirkukast, pranlukast) in the development of CSS is still debated (72, 93); we consider that these agents should be avoided in any asthma patient with eosinophilia and/or extrapulmonary manifestations compatible with smouldering CSS.

Idiopathic hypereosinophilic syndromes

The historical definition of the 'idiopathic' HES proposed by Chusid et al. in 1975 (94) empirically included: 1) a persistent eosinophilia $>1.5 \times 10^9/l$ 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 anaemia. Recent studies have demonstrated that the so-called HES represents indeed a considerably heterogeneous group of disorders, that may result especially from clonal proliferation of lymphocytes or of the eosinophils themselves (95–100).

The clinical manifestations of HES have been mainly described in older series. More common in men than in women (9 : 1), the HES occurs between the ages of 20 and 50 years (101), with an insidious onset of weakness, fatigue, cough and dyspnoea (102). The mean eosinophil count at presentation was $20.1 \times 10^9/l$ in one series (103). Nonrespiratory manifestations of the HES mainly target the skin, heart and nervous system, while eosinophilic infiltration of the liver, gastrointestinal tract, kidneys and joints may also cause symptoms (101). The skin manifestations consist of urticarial or angioedema, or erythematous and pruritic papules and nodules. The disease may involve both the central and the peripheral nervous system. Hypercoagulation may result in a variety of thromboembolic complications.

Particular attention should be paid to cardiac involvement present in 58% of the patients (102). Distinct from the eosinophilic myocarditis or coronary vasculitis observed in CSS, cardiac involvement in HES is mainly characterized by endomyocardial fibrosis, which is preceded by an acute necrotic stage, and then a thrombotic stage where intracavitary thrombi develop along the endocardium (102, 104). Although endomyocardial disease is characteristic of HES, it may be encountered in any disease that results in prolonged and marked eosinophilia (105). Endomyocardial fibrosis occurs after a duration of disease of 2 years or more and is characterized clinically by restrictive cardiomyopathy (106). The pathogenic role of eosinophil-derived cationic proteins especially MBP has been well documented (105). Echocardiography demonstrates the classic features of mural thrombus, ventricular apical obliteration and involvement of the posterior mitral leaflet (107). In addition, damage to the atrio-ventricular valves may be associated with dyspnoea, mitral (82%) and tricuspid (55%) regurgitation, cardiomegaly, and congestive heart failure (102). Sudden death due to eosinophilic myocarditis (with myocyte necrosis and apoptosis) has been reported (108).

Lung involvement present in 40% of patients (94, 102) is nonspecific and may include pleural effusion, cough and pulmonary opacities on chest CT (interstitial infiltrates, ground-glass attenuation, small nodules) (109), that should be distinguished from pulmonary oedema resulting from cardiac involvement. Cough may be the predominant feature. Eosinophilia at BAL may be mild and contrast with high-blood eosinophilia (110).

The 'lymphocytic variant' of HES (Table 3) is a T-cell disorder resulting from the production of chemokines (especially IL-5) by clonal Th2 lymphocytes bearing an aberrant CD3- CD4+ (CD2+ TCR α/β -) surface phenotype (111–113). These Th2 cells display a surface phenotype of activated memory T cells (HLA-DR+ and/or CD25+; CD45RO+) (111). Serum levels of IgE are elevated in most cases as a consequence of IL-4 and IL-13 production by Th2 lymphocytes, and polyclonal hypergammaglobulinaemia is common (112). The majority of patients are seen in dermatology clinics and present with

Table 3. Distinctive features of the lymphocytic and the myeloproliferative variants of the hypereosinophilic syndromes [adapted from Ref. (105)]

	Lymphocytic variant	Myeloproliferative variant
Pathogeny	T-cell clone producing the Th2 cytokine IL-5	<i>Fip1L1-PDGFRα</i> fusion protein resulting from interstitial deletion on chromosome 4q12
Distinctive clinical features	Skin manifestations: cutaneous papules or urticarial plaques	Male predominance Endomyocardial fibrosis Hepatomegaly, splenomegaly Mucosal ulcerations variant
Distinctive biological features	Elevated serum IgE Polyclonal hypergammaglobulinaemia Clonal peripheral lymphocytes bearing an aberrant CD3– CD4+ surface phenotype Elevated serum IL-5	Anaemia, thrombocytopenia Increased serum vitamin B12 Increased leucocyte alkaline phosphatase Circulating leucocyte precursors
Main treatment considerations	Corticosteroids Interferon- α Anti-IL-5 (mepolizumab)	Imatinib mesylate Hydroxyurea Interferon- α Anti-IL-5 (mepolizumab)

cutaneous papules or urticarial plaques infiltrated by lymphocytes and eosinophils. In some cases a cutaneous T-cell lymphoma or the Sezary syndrome may develop, as aberrant cells may undergo progressive transformation, with loss of surface TCR/CD3 expression and cytogenetic changes (such as partial 6q deletions) (114). The lymphocytic variant accounted for 16 of 60 patients with HES in a large series (111), a proportion which may be underestimated due to undetected T-cell clonality (114). Given the high frequency of skin manifestations, the lymphocytic variant of HES may resemble Gleich disease (episodic angioedema with eosinophilia) (114). Hence, lymphocyte phenotyping in search of a phenotypically aberrant T-cell subset, and analysis of the rearrangement of the T-cell receptor in search of T-cell clonality, should be performed on the peripheral blood and bone marrow as part of the routine investigation of patients with HES. In addition, IL-5 production by peripheral blood mononucleated cells or aberrant lymphocyte subsets may be measured (114). While measurement of serum IL-5 levels lacks sensitivity, serum levels of thymus and activation-regulated chemokine (TARC) seems promising (115).

The 'myeloproliferative variant' of HES has been distinguished on the basis of clinical and biological features commonly seen in chronic myeloproliferative syndromes, including hepatomegaly, splenomegaly, anaemia, thrombocytopenia, increased serum vitamin B12 and leucocyte alkaline phosphatase, and circulating leucocyte precursors (114). Cutaneous manifestations are uncommon, but mucosal ulcerations may be prominent (105, 116). Severe cardiac complications of the HES are frequent and may resist to corticosteroid therapy. Acute eosinophilic leukaemia may eventually develop (95, 101). The myeloproliferative variant of HES has been recently attributed to a constitutively activated tyrosine kinase fusion protein (*Fip1L1-PDGFR α*) due to an interstitial chromosomal deletion in 4q12 not detectable by karyotype analysis (117, 118). Imatinib, a tyrosine kinase

inhibitor originally used to treat chronic myelogenous leukaemia, proved efficient for several months in patients with HES refractory to corticosteroids, hydroxyurea and/or interferon- α .

Less than half of the patients with HES respond well to corticosteroids as a first-line therapy (1). Other treatments include chemotherapeutic agents (hydroxyurea, vincristine, etoposide), cyclosporin (101, 103), and interferon- α (119, 120), particularly in the myeloproliferative variant. Furthermore imatinib has become a major drug in patients with the myeloproliferative variant of HES, especially (but not exclusively) when the *Fip1L1-PDGFR α* fusion protein is present (117, 118). Patients with either variant of HES or HES with eosinophilic dermatitis or the mucosal ulceration form (and no characteristics of either lymphocytic or myeloproliferative variant) might respond to anti-IL-5 monoclonal antibody (mepolizumab) (19, 121, 122).

The prognosis of HES has improved markedly with about 70% survival at 10 years in recent series (102).

As the above subgroups have been described among the so-called HES, and many patients are treated before significant and potentially nonreversible organ involvement occurs, the historical criteria proposed by Chusid et al. (94) may not be appropriate anymore. The term idiopathic might henceforth be abandoned in the classification of HES (114). The lymphocytic variant of HES is a primary lymphoid disorder characterized by clonal expansion of IL-5 producing Th2 lymphocytes. The myeloproliferative variant of HES is a primary myeloproliferative disorder with characteristic cytogenetic abnormalities, and may be considered a chronic eosinophilic leukaemia. Both variants may from now on be considered as distinct entities with specific diagnostic tests, therapeutic options and prognostic considerations. A significant number of cases remain unclassified, and are in some cases related to other syndromes such as necrotizing eosinophilic vasculitis, episodic angioedema

with eosinophilia or the NERDS syndrome (nodules, eosinophilia, rheumatism, dermatitis and swelling) (105).

Parasitic eosinophilic pneumonia

Parasitic EP may be due to the infestation of humans by a variety of parasites, especially nematodes (roundworms), which may or may not be found at pathological examination of the lung. Parasite infestation represents the main cause of EP in the world. Clinical manifestations are nonspecific, and appropriate methods should be used to establish the diagnosis of parasitic EP whenever it is suspected (Table 4). A more detailed description of parasitic eosinophilic pneumonia may be found elsewhere (1).

Tropical pulmonary eosinophilia is caused by the filarial parasites *Wuchereria bancrofti* and *Brugia malayi*. Humans are infected by larvae deposited in the skin by mosquitoes. First-stage larvae or microfilariae circulate in the bloodstream and develop in 6–12 months into mature worms residing in the lymphatic vessels. The clinical features of tropical EP largely result from an immune response of the host to the antigenic constituents of circulating microfilariae trapped in the lung vasculature (123). The main symptom is cough that may be associated with fever, weight loss and anorexia (124). Chest X-ray shows bilateral disseminated opacities. Irregular basilar opacities persist after 1 year in two-thirds of patients (125). Eosinophils, and sometimes Charcot–Leyden crystals, are present in the sputum. Blood eosinophilia is prominent ($> 2 \times 10^9$ eosinophils/l) at the early stage. However, microfilariae are usually not found in the blood or the lung. Marked alveolar eosinophilia is present at BAL and drops within 2 weeks of treatment. The

diagnosis of filariasis may be established by a strongly positive serology in patients residing in an endemic area with persisting blood eosinophilia $> 3 \times 10^9$ /l, and IgE levels exceeding 10 000 ng/ml, and is further supported by clinical improvement in the weeks following treatment (1). Treatment of tropical eosinophilia is based on diethylcarbamazine; association of corticosteroids may be beneficial.

The nematode *Ascaris lumbricoides* is the most common helminth infecting humans, especially children in the tropical and subtropical areas. The disease is transmitted through food contaminated by human faeces containing parasitic eggs. Löffler syndrome may develop during the migration of the larvae of the parasite through the lung. Symptoms are usually limited to cough, wheezing, transient fever, and sometimes pruritic eruption, which resolve in a few days, while blood eosinophilic may remain elevated for several weeks (126).

Visceral larva migrans syndrome (127) caused by *Toxocara canis* may occur throughout the world. Humans and especially children become infected after ingestion of eggs released by female worms in faeces of infected dogs, often by oral contamination by the soil of public playgrounds in urban areas. The disease remains asymptomatic in a majority of cases. Fever, seizures, fatigue, and pulmonary manifestations may occur, with cough, dyspnoea, wheezes or crackles at pulmonary auscultation, and pulmonary infiltrates at chest X-ray (127). Blood eosinophilia may be present initially, or may develop only in the following days. Eosinophils are increased at BAL differential cell count. Only symptomatic treatment is recommended, while the use of antihelmintics is controversial. The pulmonary disease may occasionally be severe and necessitate mechanical ventilation; such cases may benefit from corticosteroids (128).

Strongyloides stercoralis is an intestinal nematode widely distributed in the tropical and subtropical areas. The larvae infect humans through the skin by contact with humid soil. Eosinophilia present in recently infected patients is often absent in disseminated disease (129), although *S. stercoralis* infection may persist for years. Strongyloidiasis may cause severe autoinfection and affect all organs (hyperinfection syndrome), especially in immunocompromised patients or patients treated with corticosteroids, thus presenting with fever, cough, wheezing, dyspnoea, abdominal pain, ileus, jaundice or meningitis, with or without peripheral eosinophilia, and bilateral patchy infiltrates on chest X-ray. As a consequence, treatment of all infected patients with thiabendazole is recommended. Clinical manifestations in the early stage when larvae migrate through the lungs more commonly include Löffler syndrome, EP, bronchospasm, bronchitis, and abdominal pain or diarrhoea, associated with peripheral blood eosinophilia.

EP may also occur in other infectious causes (1).

Table 4. Main parasitic causes of EP and summary of diagnostic tests

Parasites	Parasites in the faeces	Serology
In a patient who has not lived in tropical or subtropical areas		
<i>Toxocara canis</i>	–	+++
<i>Ascaris lumbricoides</i>	+++ (*)	±
In a patient who has lived in tropical or subtropical areas		
<i>Strongyloides stercoralis</i>	+++ (†)	±
<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i>	–	+++ (‡)
<i>Ancylostoma brasiliense</i> , <i>Ancylostoma duodenale</i> and <i>Necator americanus</i>	+++	+
<i>Schistosoma haematobium</i> , <i>S. mansoni</i>	–/+++ (§)	++

*Only 3 months after pulmonary manifestations; larvae may be found in sputum or gastric aspirates.

†Larvae may be found in sputum, bronchial washing and BAL fluid.

‡Microfilariae may occasionally be found.

§Parasites may be found in urine (*S. haematobium*) or biopsy of the rectum (*S. haematobium*, *S. mansoni*).

Allergic bronchopulmonary mycosis and bronchocentric granulomatosis

An extensive review on ABPA can be found elsewhere in this series (130). ABPA results from a complex allergic and immune reaction in the bronchi and the surrounding lung parenchyma in response to antigens from *Aspergillus* colonizing the airways of asthmatics. Allergic bronchopulmonary disease may also be produced by fungi other than *Aspergillus*, such as *Pseudallescheria boydii*, *Cladosporium herbarum*, *Candida albicans*, etc. (2). The immunological response to *Aspergillus* schematically combines both type I and type III hypersensitivity (mediated by immunoglobulins E and G, respectively), and results over time in damage to the bronchial and pulmonary tissue (131). Mucous plugs containing *Aspergillus* obstruct the airways with subsequent atelectasis and bronchial wall damage and proximal bronchiectasis predominating in the upper lobes (132–134). The presence of bronchiectasis in three or more lobes in asthmatics (well visualized on CT) is highly suggestive of ABPA, especially when associated with centrilobular nodules and mucoid impaction (135); thus a correct diagnosis of ABPA was made on CT scan in 84% of cases with ABPA in a series of patients with eosinophilic lung diseases (58). EP may be found incidentally in resection specimens of chronic pulmonary consolidation from patients with asthma and ABPA (132).

ABPA occurs mainly in adults with preexisting asthma, as well as in up to 7.8% (136) of patients with cystic fibrosis. Interestingly, an increased prevalence of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations has been reported in noncystic fibrosis patients with ABPA (137, 138), suggesting that such mutations could be involved in the development of ABPA without overt cystic fibrosis. Of note, allergic *Aspergillus* sinusitis is considered to have a pathophysiology similar to that of ABPA (139, 140); both diseases may be associated in a syndrome called sinobronchial allergic aspergillosis.

The early stage of ABPA is characterized by fever, expectoration of mucus plugs containing eosinophils and Charcot–Leyden crystals, peripheral blood eosinophilia $>1 \times 10^9/l$, and pulmonary infiltrates due to EP, or segmental or lobar atelectasis due to mucus plugging (141). Chronic ABPA is characterized by asthma, eosinophilia, and bronchopulmonary manifestations including bronchiectasis (when the latter is lacking, cases are designated as ABPA-seropositive) (142). The current diagnostic criteria include asthma, history of pulmonary infiltrates, proximal bronchiectasis, elevated serum immunoglobulin E, and immunological hypersensitivity to *A. fumigatus* such as immediate reaction to prick test for *Aspergillus* antigen, precipitating antibodies against *A. fumigatus*, and elevated specific immunoglobulin E against *A. fumigatus* (with approximately 40 antigenic components identified to date) (142, 143). The expecto-

ration of mucous plugs, the presence of *Aspergillus* in sputum, and late skin reactivity to *Aspergillus* antigen are also common at this stage (143).

The treatment of exacerbations of ABPA relies on corticosteroids and may contribute to preventing the progression of the disease to the fibrotic end stage (144). Long-term corticosteroid therapy is required only in patients with progressive lung damage or frequent symptomatic attacks (142). Inhaled corticosteroids may reduce the need for long-term oral corticosteroids. Oral itraconazole allows the reduction of the doses of corticosteroids and is a useful adjunct to corticosteroids (145, 146). Treatment with itraconazole allows reduction of the corticosteroid oral dose (147), improves immunological surrogates of disease, and reduces the rate of exacerbations as compared with placebo (148), but its long-term effect on lung function is unknown (149). Treatment with voriconazole has not yet been evaluated in ABPA.

Bronchocentric granulomatosis is a granulomatous inflammatory and destructive process with peribronchiolar predominance (150). Scattered fungal hyphae may be demonstrated by the Grocott silver stain in some patients. A dense inflammatory infiltrate with a predominant eosinophilic component (especially in asthmatic patients) is generally present in the peribronchial tissue and sometimes the more distal lung parenchyma, occasionally with vascular inflammation and mucoid impaction (151). About half the patients are asthmatics. They further present with fever and cough, peripheral blood eosinophilia. Imaging abnormalities include masses, reticulonodular opacities, or alveolar infiltrates or consolidations predominating in the upper lobes and unilateral in a majority of patients (152, 153). Most of these patients fulfil the criteria for ABPA, and respond well to corticosteroids despite frequent recurrences. Eosinophilia is usually conspicuous only when bronchocentric granulomatosis occurs in asthmatic patients.

Eosinophilic pneumonias secondary to drug, toxic agents and radiation therapy

All drugs taken in the weeks or months preceding the clinical syndrome of EP must be thoroughly investigated, including illicit drugs (cocaine or heroin). Although EP has been reported in association with more than 80 drugs, the causality has not been established for many of them, thus limiting to fewer than 20 the number of drugs which can definitely be considered as a common cause of EP. Out of these drugs, many are nonsteroidal anti-inflammatory drugs or antibiotics (Table 5).

Drug-induced EP may develop progressively (chronic EP) with increasing dyspnoea, cough and mild fever in a subject who has been taking a drug for several months or years. Alternatively, it may present as transient pulmonary infiltrates with eosinophilia (Löffler syndrome) discovered by systematic chest X-ray in poorly symptomatic

Table 5. Drugs which cause typical eosinophilic pneumonia [from Ref. (1)]

Acetylsalicylic acid
Captopril
Diclofenac
Ethambutol
Fenbufen
Granulocyte monocyte-colony stimulating factor
Ibuprofen
L-Tryptophan
Minocycline
Naproxen
<i>Para</i> -(4)-aminosalicylic acid
Penicillins
Phenylbutazone
Piroxicam
Pyrimethamine
Sulindac
Sulphamides-sulphonamides
Tolfenamic acid
Trimethoprim-sulphamethoxazole

patients. Lastly, some patients present with acute EP sometimes requiring mechanical ventilation.

The only absolute proof that a drug is responsible of EP might theoretically be obtained by its reintroduction with ensuing relapse of pneumonia, but this approach is dangerous. The regression of EP after stopping the drug is a good clue for its iatrogenic cause, but corticosteroids are often given concomitantly with drug withdrawal to accelerate clinical improvement, so that the responsibility of the drug cannot be definitely established. When present, cutaneous rash or pleural effusion increase the likelihood of the diagnosis. Associated extrapulmonary iatrogenic manifestations such as systemic eosinophilic vasculitis (thus mimicking CSS) have been reported (154, 155).

Respiratory manifestations characteristic of EP were also observed during the so-called eosinophilia-myalgia syndrome related to the intake of contaminated preparations of L-tryptophan (156), as well as the toxic-oil syndrome resulting from the ingestion of denatured cooking oil (157).

Similar to what seen with the organizing pneumonia syndrome that may be primed by radiation therapy (158), chronic EP similar to ICEP has been described after radiation therapy for breast cancer (159) in women. All patients had a history of asthma and/or allergy. All patients were symptomatic at the onset of EP, with dyspnoea and cough developing 1–10 months after the completion of radiation therapy (median 3.5 months). Chest radiograph showed pulmonary infiltrates, unilateral and limited to the irradiated lung, or bilateral, and migratory in some cases. A causal relationship between radiation therapy and EP was supported by the first appearance of pulmonary opacities within irradiated areas. All patients had blood eosinophilia $>1 \times 10^9/l$ and/or eosinophilia 40% or higher at BAL differential cell count. A careful search identified no parasitic

infection or drugs that could have caused eosinophilic pneumonia. Oral corticosteroid treatment allowed rapid clinical and radiologic recovery without sequelae in all patients, but relapse occurred after treatment withdrawal in some patients. The time course of the disease was compatible with a role of radiation therapy, as previous studies have demonstrated that radiation-induced organizing pneumonia may develop within a year after the completion of radiation therapy (158). Although a causal relationship between radiation therapy and EP could not be definitely established from this descriptive study, it may be hypothesized (159) that priming of alveolitis by radiation to the breast may result in either chronic EP or organizing pneumonia, depending on genetic or acquired characteristics of patients and/or further triggering factors. Among patients who undergo radiation therapy for breast cancer, those with a history of asthma or atopy might preferentially develop EP rather than organizing pneumonia.

Miscellaneous lung diseases with associated eosinophilia

Blood and/or BAL eosinophilia may be present in other bronchopulmonary disorders where EP is not prominent.

Eosinophilic inflammation of the airways is a major pathological feature of asthma. Some mild increase of eosinophils at BAL differential cell count (usually fewer than 5%) may be found in asthma (160). Monitoring of the sputum eosinophil count may help in adapting the treatment and reducing asthma exacerbations and hospital admissions (161).

Eosinophilic bronchitis (without asthma) with a high percentage of eosinophils (about 40%) in sputum is a well-recognized cause of chronic cough responsive to corticosteroid treatment (162–164). Eosinophils are increased within the airways in eosinophilic bronchitis to levels similar to those found in asthma (165). Patients usually have normal lung function and airway responsiveness in comparison with asthmatic patients (166). However, the development over time of irreversible airflow obstruction has been reported in a patient with eosinophilic bronchitis without asthma (167), and repeated episodes of eosinophilic bronchitis are associated with the development of chronic airflow obstruction, including asthma (168). Whether eosinophilic bronchitis is a distinct clinical entity or just represents a precursor of asthma remains unknown (169). Chronic bronchiolitis associated with obstructive ventilatory defect and histopathological eosinophilic lung infiltrates has been reported (170).

Mildly increased levels of eosinophils may be found at BAL differential cell count in idiopathic interstitial pneumonias, a finding associated with a poor prognosis in idiopathic pulmonary fibrosis (171–173). Focal EP has been reported in cases of usual interstitial pneumonia (174). The typical clinical and imaging features of

cryptogenic organizing pneumonia may closely mimic ICEP (175), and some clinical or pathological overlap may be encountered between these two diseases. Pulmonary Langerhans cell histiocytosis granulomatosis (also designated as eosinophilic granuloma) is characterized by proliferating Langerhans cells, and granulomatous lesions that may be rich in eosinophils especially at the initial active stage of the disease in about 25% of cases

(176, 177). Blood eosinophilia and tissue eosinophilia may be present in sarcoidosis, but are usually mild (178). In lung transplant recipients, pulmonary eosinophilia may result from infectious agents such as *Aspergillus*, *Pseudomonas* or coxsackie virus (179), but it may be indicative of acute rejection (179, 180). EP was reported in a patient with gastric cancer producing GM-CSF and IL-5 (181).

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