HYPEREOSINOPHILIC OBLITERATIVE BRONCHIOLITIS:

A DISTINCT, UNRECOGNISED SYNDROME

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ABSTRACT (200 words, limit 200 words)

Background: Only isolated biopsy-proven cases of eosinophilic bronchiolitis have been reported, all from Japan.

Methods: We present 6 patients with hypereosinophilic obliterative bronchiolitis (HOB), defined by the following criteria: 1-blood eosinophil cell count >1G/L and/or BAL eosinophil count >25%, 2-persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids, 3-eosinophilic bronchiolitis at lung biopsy (n=2) and/or direct signs of bronchiolitis (centrilobular nodules, branching opacities) on computed tomography (n=6).

Results: Chronic dyspnea and cough often severe, without the characteristic features of asthma, were the main clinical manifestations. Atopy and asthma were present in the history of 3 and 2 patients, respectively. One patient met biological criteria of the lymphoid variant of idiopathic hypereosinophilic syndrome. Mean blood eosinophil cell count was 2.7 G/L and mean eosinophil differential percentage at bronchoalveolar lavage was 63%. Mean initial FEV1/FVC ratio was 50%, normalising with oral corticosteroid therapy in all patients. HOB manifestations recurred when oral prednisone was decreased to 10-20 mg/day, but higher doses controlled the disease.

Conclusion: HOB is a characteristic entity deserving to be individualised among the eosinophilic respiratory disorders. Thorough analysis is needed to determine whether unrecognised and/or smouldering HOB may further be a cause of irreversible airflow obstruction in chronic eosinophilic respiratory diseases.

KEYWORDS: Bronchiolitis; Eosinophilic lung disease; Allergic bronchopulmonary aspergillosis; Churg-Strauss syndrome; Eosinophilic pneumonia; Asthma
The spectrum of eosinophilic bronchopulmonary diseases [1], either primary or secondary, especially comprises parenchymal disorders (acute and chronic eosinophilic pneumonias), and eosinophilic airway disorders, including eosinophilic bronchitis and the eosinophilic phenotype of asthma. Some eosinophilic disorders, such as allergic bronchopulmonary aspergillosis (ABPA) and Churg-Strauss syndrome (CSS), may involve both parenchymal and airways structures[2].

Eosinophilic bronchiolitis has been reported in a non-asthmatic Japanese patient [3], with a 3-year history of diffuse pan-bronchiolitis, who developed blood (6.9 G/L) and alveolar eosinophilia (with 91% eosinophils in bronchoalveolar lavage [BAL]) as well as airflow obstruction. High-resolution computed tomography (HRCT) revealed diffuse, poorly-defined centrilobular nodules, thickening of bronchial and bronchiolar walls, and mild bronchiectasis; lung biopsy disclosed eosinophilic bronchiolitis. Airflow obstruction improved with corticosteroids but relapsed upon tapering. A few additional isolated cases, all from Japan, have been described in another report [4]. However, whether eosinophilic bronchiolitis corresponds to a specific condition has not been established.

In this article, we present 6 patients with a relevant clinical, radiological, and functional syndrome, who cannot be classified into any recognised condition and who especially manifested features quite distinct from eosinophilic asthma. We further propose the term hypereosinophilic obliterative bronchiolitis (HOB) and suggest provisional working diagnostic criteria to delineate the condition.

**MATERIALS AND METHODS**

*Definition of cases*
HOB diagnosis included the following 3 criteria:

1. Blood eosinophil cell count >1 G/L (and/or BAL eosinophil differential cell count >25%).

2. Persistent airflow obstruction on lung function tests, defined by post-bronchodilator forced expiratory volume in 1 s (FEV1) / forced volume capacity (FVC) ratio <70% and FEV1 <80% of predicted values, not improved by 4-6 weeks of inhaled corticosteroid therapy (2,000 µg/day of beclometasone or equivalent). Other functional features of obliterative bronchiolitis may comprise decreased forced expiratory flow between 25 and 75% of FVC (FEF25-75), and increased residual volume (RV) to total lung capacity (TLC) ratio.

3. Lung biopsy demonstrating inflammatory bronchiolitis with prominent bronchiolar wall infiltration by eosinophils (associated or not with alveolar and/or vessel infiltration by eosinophils) and/or characteristic direct HRCT features of bronchiolitis, as defined below.

Pulmonary function tests were performed according to European Respiratory Society recommendations.

**Imaging**

All patients underwent chest X-rays and spiral HRCT in the imaging department of our hospital with a multidetector CT system (Philips B64, Eindhoven, The Netherlands). All HRCT data were reviewed collectively by 3 authors (DR, JFC, VC); independent review of HRCT data by another radiologist (CP) showed agreement on 88% of items of direct
bronchiolitis features. Maximum intensity projection post-processing [5] was performed to improve the detection of centrilobular nodules. Imaging features were described according to the Fleishner Society guidelines [6]. Direct features of bronchiolitis were the following: poorly-defined centrilobular nodules, branching opacities, and tree-in-bud pattern. Indirect signs of bronchiolitis were mosaic attenuation on inspiratory CT and air-trapping pattern on end-expiration CT consisting of a patchwork of regions of differing attenuation, and bronchial wall thickening.

Study design

Data were acquired retrospectively. According to French legislation, informed consent is not required for retrospective data collection corresponding to current practice. However, the database was anonymous and complied with requirements of the Commission nationale de l’informatique et des libertés, the organisation dedicated to privacy, information technology, and civil rights in France.

RESULTS

Individual cases

The clinical features of 6 patients are reported below, with further history and investigations, lung function tests and HRCT findings presented in Tables 1, 2, and 3, respectively.

Patient #1

A 46-year-old man presented in August 2011 with persistent, chronic, exhausting cough. Spirometry was normal. He was given oral corticosteroid therapy (OCST) over a few weeks with disappearance of the cough. Shortly after stopping OCST, severe cough relapsed with
further dyspnea and airflow obstruction on pulmonary function tests. Blood eosinophil count was 1.9 G/L, and BAL differential cell count was 50% eosinophils. Blood analysis disclosed that 7.8% of total lymphocytes had a CD3+ CD4+ CD7- surface immunophenotype with further oligoclonal (175-183-193 bp) T-cell receptor gamma VG9J1J2 re-arrangement. HRCT demonstrated direct bronchiolitis features (Figure 1). Oral prednisone was resumed and decreased progressively from 40 to 10 mg/day. The patient was thereafter asymptomatic with normal lung function.

Patient #2

A 41-year-old woman presented in June 2007 with nasal congestion, severe, permanent cough with viscous mucous sputum and occasional wheezing. In March 2008, her symptoms persisted despite intermittent OCST. Spirometry and HRCT were normal. Fiberoptic bronchoscopy disclosed small, whitish mucosal granulations disseminated over the mucosa of the trachea and main bronchi (Figure 2). Blood eosinophil count was 1.5 G/L, and BAL differential count was 15% eosinophils. Inhaled budesonide (400 µg x 3/day) resulted in clinical improvement. A diagnosis of eosinophilic bronchitis was considered. She was lost to follow-up, and received various treatments, including methotrexate, in addition to OCST; however, the clinical manifestations relapsed as soon as prednisone was decreased below 20 mg/day. In May 2010, the patient manifested severe airflow obstruction and hypoxaemia as well as direct HRCT features of bronchiolitis. Blood eosinophil count was 1.4 G/L, and BAL differential cell count was 60% eosinophils. She received 40 mg prednisone/day progressively with major clinical and functional improvement. Treatment was tapered, but dyspnea and airflow obstruction re-appeared at a dose of 25 mg/day of prednisone. The patient was started on omalizumab off-label (total IgE level was 150 mg/L), with better control of symptoms allowing tapering of prednisone to alternate daily doses of 10 and 15 mg/day. Again, lung
function deteriorated, FEV1 decreased from 3.1 (111%) to 2.3 L (83%), and eosinophil count increased to 0.8 G/L. Azathioprine (150 mg/day) was added, and prednisone augmented to 15 mg/day, resulting in FEV1 correction (2.9 L) within 3 months. At last control in June 2012, FEV1 was 2.43L (89%) despite 17.5 mg/day of prednisone.

Patient #3

A 47-year-old man with a history of exercise asthma since 1994 (controlled by inhaled corticosteroid and bronchodilator) presented in May 2009 with increasingly severe cough and migratory pulmonary opacities, mild features of bronchiolitis on chest imaging and elevated eosinophil blood cell count (2.7 G/L). In October 2009, dyspnea intensified, with airflow obstruction (Table 2). HRCT demonstrated direct bronchiolitis features with further bronchiectasis and mucous plugging (Figure 3). Multiple whitish nodules of the mucosa of the trachea and of most bronchi were apparent on fiberoptic bronchoscopy: biopsy disclosed ulcerated mucosa with areas of necrosis and prominent eosinophilic inflammation. Peripheral eosinophil blood cell count was 2.2 G/L, and BAL differential cell count was 69% eosinophils. No bacteria, fungi, or moulds were evident on either direct examination and culture. Treatment with 40 mg of oral prednisone was initiated with rapid clinical and functional improvement. Progressive decrease of the prednisone dose to 10 and 15 mg/day every other day provided suboptimal clinical control, with FEV1 of 3.3 L (86%) and blood eosinophil cell count of 0.8 G/L. The patient informed us that he had stopped inhaled corticosteroids for several months. Resuming inhaled therapy (with unchanged dose of prednisone) normalised FEV1 (4.5 L, 118% of predicted value).

Patient #4

A 44-year-old non-asthmatic woman presented at another institution in 2005 with persistent, productive cough. Alveolar consolidation was seen in the right middle lobe on imaging.
Peripheral blood eosinophil count was 2.9 G/L, with 78% eosinophils on BAL differential cell count. Retrospectively, she was found to have a long-standing history of blood eosinophilia, with 0.9 G/L eosinophils in 1998. When she was referred for evaluation, peripheral eosinophils were 2 G/L, and airflow was obstructed (Table 2). HRCT revealed direct bronchiolitis features. The patient improved rapidly on OCST, with long-term stable lung function while taking less than 10 mg/day of prednisone. In April 2012, while on 5 mg/day of oral prednisone, FEV1 was slightly impaired and eosinophil blood cell count was 1.04 G/L.

**Patient #5**

A 46-year-old woman was referred in September 2007 for progressive dyspnea over the past 6 months despite inhaled bronchodilator and high-dose inhaled corticosteroid. Airflow was found to be severely obstructed on lung function tests, and the 6-minute walk test distance was only 278 m. Peripheral blood eosinophil count was 2.4 G/L, and BAL differential cell count was 35% eosinophils. HRCT demonstrated direct bronchiolitis features. OCST resulted in rapid improvement of both symptoms and lung function (Table 2). However, airflow obstruction recurred with tapering of OCST.

**Patient #6**

A 40-year-old man presented in November 1991 with intermittent cough, progressive dyspnea, and airflow obstruction (Table 2). In February 1992, symptoms and airflow obstruction worsened. Peripheral blood eosinophil count was 5.4 G/L, and BAL differential cell count was 85% eosinophils. Infiltrative opacities were apparent on chest X-ray. Lung biopsy in March 1992 was reported as “diffuse eosinophilic bronchioloalveolitis”. OCST, initiated at 60 mg/day of oral prednisolone, normalised lung function 1 month later. However, OCST could not be decreased below 15 mg/day because of relapsing bronchopulmonary
manifestations and airflow obstruction. The patient received various treatments in addition to OCST in other institutions, including hydroxycarbamide, imatinib, and alpha-interferon.

In February 2006, blood eosinophil differential count was 18% while he was receiving 17.5 mg/day of oral prednisolone. In February 2010, severe airflow obstruction persisted on 15 mg/day of prednisolone, inhaled fluticasone 500 µg - salmeterol 50 µg twice a day, and 500 mg/day of hydroxycarbamide. The conclusion of lung biopsy review was: diffuse eosinophilic pulmonary disease with eosinophilic granulomatous vasculitis involving the small arteries and capillaries, eosinophilic bronchiolitis severely impairing the bronchiolar walls with intraluminal eosinophilia (Figure 4), and eosinophilic alveolitis with eosinophilic abscesses, compatible with a diagnosis of ‘lung-limited CSS’. Airflow obstruction progressively worsened subsequently despite OCST greater than 15 mg/day of prednisone. Transient increase in OCST (50 mg/day for 3 weeks, then 40 mg/day for 3 weeks) resulted in major functional improvement at last visit (table 2).

**Group analysis**

*Clinical manifestations and lung function*

The respiratory manifestations were clearly distinct from those of asthma, and patients especially did not have recurrent paroxystic symptoms of dyspnea and wheezing (asthma attacks). Cough often severe and acute or chronic dyspnea (with transient control while under short-term OCST) were the major symptoms. Airflow was obstructed in all patients (Table 2). The response to inhaled short-acting bronchodilators was significant in 2/6 patients, but lung function did not normalise in any patients with prolonged therapy involving inhaled long-acting bronchodilators and high-dose inhaled corticosteroids. In contrast, OCST resulted in correction of airflow obstruction in all cases.
No patient presented extra-respiratory, eosinophil-related, systemic manifestations. No clinical criteria of pulmonary, especially viral, infections were apparent at diagnosis. No patients were taking drugs with possible iatrogenic eosinophilic outcomes.

**Biological findings**

Mean eosinophil blood cell count was 2.6 G/L (range 1.4-5.4 G/L) at HOB diagnosis, and the BAL eosinophil differential cell count was 63% (range 35-85%). C-reactive protein level was elevated in only 1 patient. Stool analysis and serologies for parasitic infections were negative in all patients. Systematic immunological testing included antinuclear antibodies (all negative), antineutrophil cytoplasmic antibodies (all negative), rheumatoid factor (positive in 3/6), and anti-citrullinated peptide antibodies (positive with a low titer in 1/6). No patients met diagnostic criteria for connective tissue disease or systemic vasculitis. Total IgE was elevated in 5/6 cases. IgE specific to *Aspergillus fumigatus* was negative in all cases except patient #6, who did not fulfill the diagnostic criteria of ABPA. Skin tests for *Aspergillus* were negative in 5/5 patients. T-cell clonality was found in 1/6 patients (patient #1, see above). FIP1L1-PDGFRα and Bcr-abl fusion transcripts and Jak2 mutations were present in 0/6, 0/3 and 0/3 cases, respectively. Serum interleukin-5 level was elevated in 1/6 cases. Tryptase and vitamin B12 serum levels were normal in 6/6 and 5/5 cases, respectively.

**Imaging**

Chest X-ray did not generally contribute to the diagnosis of HOB, but showed a finger-in-glove sign in the right upper lobe in patient #3. Direct signs of bronchiolitis were the predominating abnormal features on HRCT in all patients, with ill-defined centrilobular nodules of ground glass attenuation (6/6), branching opacities (V-shaped or Y-shaped) (6/6), and tree-in-bud pattern (5/6) (Table 3). Mosaic attenuation was apparent on inspiratory CT in 2 patients, and air trapping was observed on end-expiratory CT in 2 patients tested. Limited
areas of ground glass attenuation or consolidation were seen in 2 patients, and bronchial abnormalities, especially bronchial wall thickening, were noted in 5 patients. The finger-in-glove sign was discerned on HRCT in patient #3, with mucus density measurements ranging from 42 to 63 Hounsfield units (HU) and mucus plugs of similar density as that of skeletal muscles. Mildly-enlarged mediastinal lymph nodes (>10 mm) were present in all patients. No patient had pleural or pericardial effusion. Sinus imaging in all patients showed pan-sinusitis in 2 cases and para-sinusal and frontal sinusitis in 2 cases.

Follow-up

OCST, initiated at a median dose of 0.7 mg.kg/day of prednisone (range 0.5-1.1 mg/kg/day), resulted in rapid improvement of clinical manifestations in all patients, with a dramatic fall in blood eosinophil cell count to normal values. Functional improvement was dramatic upon OCST in all cases. The FEV1/FVC ratio returned to normal in all patients on corticosteroid therapy, with a median FEV1 increase of 1.7 L. Complete or near-complete resolution of direct HRCT signs of bronchiolitis on HRCT was obtained in all patients, who were followed for a median of 58 months (range 10-247 months). Airflow obstruction recurred 5 times in patient #2 while receiving 12.5 mg/day of prednisone, and 5 and 4 times respectively in patients #4 and #5 after they had interrupted OCST. At last visit, all patients were still receiving OCST with a median dose of 10 mg/day (range, 2.5 – 12.5), and all were on inhaled corticosteroids and bronchodilators. Airflow obstruction, despite inhaled therapy, was present only in patient #6 with poor compliance with therapy. In 1 patient, azathioprine and off-label omalizumab were initiated because of recurrent airflow obstruction despite a daily prednisone dose exceeding 20 mg/day.
DISCUSSION

The above cases share common characteristics which collectively delineate a distinct entity deserving recognition as an original syndrome. We propose the term HOB to describe this entity, defined by: 1) blood hypereosinophilia above 1 G/L and/or BAL eosinophilia >25%; 2) airflow obstruction not improved by prolonged course of inhaled bronchodilators and corticosteroids; 3) and characteristic direct signs of bronchiolitis on HRCT imaging and/or at lung biopsy. Of note, peripheral blood eosinophilia surpassed 1.5 G/L, and BAL eosinophilia was >40% in 5/6 cases, indicating that HOB is characterised by really marked eosinophilia (“hypereosinophilia”), and these thresholds may be appropriate as future diagnostic criteria.

Bronchiolitis [7] is defined pathologically as a bronchiolar cellular inflammatory process with further possible bronchiolar fibrosis. A limitation of this study was that a lung biopsy was not mandatory for the diagnosis of bronchiolitis, provided that both airflow obstruction and characteristic direct signs of bronchiolitis on HRCT were present [6, 8, 9]. Although a definitive diagnosis of bronchiolitis relies on biopsy, this invasive procedure is currently rarely performed in such a setting. The terms bronchiolitis obliterans and obliterative bronchiolitis are considered to be synonymous, however we usually employ the term obliterative bronchiolitis to designate the clinical functional condition characterised by airflow obstruction resulting from bronchiolitis [10], while the pathological condition is usually designated bronchiolitis obliterans. The characteristic CT direct features of bronchiolitis have been well established [8], with i) a pattern of ill-defined nodules of ground glass attenuation (observed in subacute hypersensitivity pneumonitis and CSS) and corresponding pathologically to peribronchiolar inflammation; and ii) a pattern of centrilobular nodules with a tree-in-bud appearance and bronchial wall thickening (as seen in *Mycobacterium* infection and ABPA), which correspond pathologically to the plugging of
small airways or dilated bronchioles. The imaging pattern in HOB fitted the characteristic features of the latter. A mosaic pattern on inspiratory CT (an indirect feature of bronchiolitis) [6, 7, 11] was less frequent.

We consider that the cases reported above support the opinion that HOB is a syndrome, i.e. a group of symptoms and signs constituting a distinct clinical individuality without any univocal cause. HOB may be idiopathic, associated asthma, or part of an established condition of either unknown (e.g. CSS or clonal hypereosinophilic syndrome) or determined cause (e.g. ABPA or drug reaction).

HOB comprises distinctive features generally not observed in asthma, including imaging of bronchiolitis and a protracted course not responding to inhaled therapy. However, eosinophilic asthma and HOB may belong to the same spectrum of conditions, and it is likely that some HOB cases may previously have been considered as severe, persistent asthma with particularly high eosinophilia and requiring prolonged OCST. Asthma might precede HOB in some cases, as in patient #2. Centrilobular opacities have been reported in 21% of 50 asthmatic patients, more frequently in those with the most severe asthma [12]. Nasal polyposis, a hallmark of eosinophilic asthma [13], was apparent and severe (requiring surgery) in 2 patients. We have previously proposed to define hypereosinophilic asthma by the association of asthma and blood eosinophil cell count >1 G/L (especially >1.5 G/L) and/or eosinophils >25% (especially >40%) at BAL differential cell count [14]. Hypereosinophilic asthma may be isolated or related to determined causes (iatrogenic, parasitic infections, ABPA) or conditions of unknown etiology (idiopathic chronic eosinophilic pneumonia, CSS) [2, 14], and may lead to fixed airflow [15]. Recognising HOB and distinguishing it from asthma is worthwhile, as dramatic improvement is obtained by OCST, which may need to be continued on the long-term to control airflow obstruction. Clearly, more attention should be
paid in the future to searching for HOB features in patients with hypereosinophilic asthma as defined above. Interestingly, patients with the recently reported condition of asthmatic granulomatosis did not fit the criteria of HOB, with blood eosinophilia > 1 G/L in only 2 of 10 patients, airflow obstruction in 6 of 10, and tree-in-bud at HRCT in only 1 of 10 patients [16].

Prominent bronchial wall thickening in 5/6 patients was also present in Japanese cases of eosinophilic bronchiolitis [3, 4]. Whitish tracheal and bronchial granulations were present in 2 patients, a finding seldom reported in eosinophilic lung disorders [17, 18], with ulcerative lesions and prominent eosinophilia at bronchial biopsy in 1 patient.

HOB was idiopathic in 5/6 cases and coupled with the lymphoid variant of the hypereosinophilic syndrome in 1 case [1, 19], indicating that HOB may be a syndrome present in various conditions. HOB also shares some similarities with ABPA, with centrilobular nodules reported in 73-93% of patients [20, 21], and commonly bronchial wall thickening and mucus plugging with ‘finger-in-glove’ pattern [22]. Bronchiectasis was present in only HOB patient #3, but it can occur late in the course of ABPA [20]. The bronchial HRCT features in patient #3 were suggestive of ABPA with upper lobe central bronchiectasis with mucoid impaction (finger-in-glove sign). However, the skin prick test for Aspergillus was negative, and IgE level was below 500 IU/L, thus theoretically excluding ABPA, although IgG and IgE specific to Aspergillus were slightly positive. Immunology features diagnostic of ABPA were not evident in the other HOB patients, and Aspergillus was not detected in BAL, sputum, or lung biopsy.

Similarly, it is conceivable that HOB syndrome may be found in patients with CSS. HRCT abnormalities in CSS include centrilobular nodules, bronchial wall thickening, and bronchiectasis [2, 23-25], with the individualisation of 2 distinct imaging patterns: an airway
pattern (consisting of small centrilobular nodules and bud-in-tree sign, bronchial dilation, bronchial wall thickening, and mosaic perfusion), and an airspace pattern (ground glass opacities, consolidation, and poorly-defined nodules) [24]. Anomalies in HOB were very similar to the airway HRCT pattern reported in CSS, which is associated with airflow obstruction [24]. The classic pathological features of CSS including a combination of eosinophilic infiltration, granulomatous inflammation, and vasculitis, were present in patient #6, indicating a diagnosis of ‘lung-limited CSS’. Airflow obstruction was persistent in 38% of CSS patients with more than 3 years of follow-up [26]. These observations collectively suggest that features compatible with HOB are common in patients with CSS.

We previously noted the case of a 28-year-old man who developed cough, dyspnea, fever, and airflow obstruction while taking minocycline [27], with ground glass opacities, peribronchovascular thickening, and micronodules compatible with bronchiolitis at CT. Blood cell count was 1.6 G/L, and BAL differential cell count was 39% eosinophils. Retrospectively, we consider that this patient likely had iatrogenic HOB.

OCST was required in all patients because of persistent airflow obstruction. Clinical and functional improvement was spectacular on OCST, with complete remission of airflow obstruction, whereas a prolonged course of inhaled bronchodilators and corticosteroids did not prevent gradual worsening of the disease. OCST nevertheless needed to be continued over the long-term, because of relapses (often progressive and insidious) when decreasing the daily doses of prednisone below 10-20 mg, which indicates that chronic HOB might be a cause of chronic, persistent airflow obstruction in eosinophilic lung diseases. Persistent airflow obstruction may significantly improve with increased doses of OCST for several weeks, as shown in patient #6. Our provisional approach to HOB treatment consists of OCST (in addition to inhaled bronchodilators and corticosteroids) at an initiating dose of ~0.75
mg/kg/day to rapidly normalise lung function, then decreased progressively over a few weeks with tight monitoring of both spirometry and blood eosinophil cell count to eventually adjust the dose to the lowest sufficient level, similar to the ‘tight control’ step-down strategy in rheumatoid arthritis [28].

Whether untreated or undertreated smouldering HOB may result in irreversible airflow obstruction is not presently known. Larger studies are needed to address this question and to further determine if irreversible airflow obstruction, observed in some patients with disorders such as ABPA [20], CSS [26], idiopathic chronic eosinophilic pneumonia [29], or eosinophilic bronchitis [30], may derive from chronic and/or smouldering HOB.

Acknowledgements

We thank M.L. Braud, L. Chalabreysse, B. Hohn, C. Massot, D. Rigaud, S. Turquier and L. Vassort for referring patients, communicating appropriate information as requested, and participating in patient diagnosis and management.
### Table 1. History and investigations

<table>
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<th>Patient number</th>
<th>History of atopy and/or asthma</th>
<th>Nasal polyposis</th>
<th>Skin tests</th>
<th>Total IgE(^1) (highest value)</th>
<th>Aspergillus fumigatus antibodies (IgG, IgE)</th>
<th>Smoking (quit)</th>
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<td>Patient #1</td>
<td>Conjunctivitis and rhinosinusitis in childhood (desensitisation)</td>
<td></td>
<td>Positive (grass, short ragweed) Negative for AF</td>
<td>1,709 kU/L</td>
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<td>90 kU/L</td>
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<td>Patient #3</td>
<td>Rhinitis in childhood Exercise asthma Nasal polyposis requiring surgery</td>
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<td>Positive (grass) Negative for AF</td>
<td>486 kU/L</td>
<td>07.09 negative 02.2012 positive</td>
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<td>Patient #4</td>
<td>Chronic cough, possible asthma Nasal polyposis requiring surgery</td>
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<td>391 IU/mL</td>
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<td>101 kU/L</td>
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<td>920 kU/L</td>
<td>IgE-positive AF m(^3) 3.58 (N &lt;0.10) IgG-negative</td>
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AF: *Aspergillus fumigatus*, PY: pack-years

\(^1\) Normal IgE values are less than 150 kU/L or less than 391 IU/mL
Table 2. Selected lung function tests

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<tr>
<th>Patient #1</th>
<th>Date (day.month.year)</th>
<th>FEV1 (L) (% predicted)</th>
<th>FEV1 (L) post-bronchodilator</th>
<th>FEV1/FVC (%)</th>
<th>FEF25-75 (L.s(^{-1})) (% predicted)</th>
<th>RV/TLC (%)</th>
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<th>FEV1 (L) post-bronchodilator</th>
<th>FEV1/FVC (%)</th>
<th>FEF25-75 (L.s(^{-1})) (% predicted)</th>
<th>RV/TLC (%)</th>
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<td>27.06.2012</td>
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<th>FEV1 (L) post-bronchodilator</th>
<th>FEV1/FVC (%)</th>
<th>FEF25-75 (L.s(^{-1})) (% predicted)</th>
<th>RV/TLC (%)</th>
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<td>2.68</td>
<td>58</td>
<td>1.34 (32)</td>
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<td></td>
<td>17.02.2010</td>
<td>3.93 (103)</td>
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<td>67</td>
<td>2.47 (60)</td>
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<table>
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<tr>
<th>Patient #4</th>
<th>Date (day.month.year)</th>
<th>FEV1 (L) (% predicted)</th>
<th>FEV1 (L) post-bronchodilator</th>
<th>FEV1/FVC (%)</th>
<th>FEF25-75 (L.s(^{-1})) (% predicted)</th>
<th>RV/TLC (%)</th>
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<tbody>
<tr>
<td></td>
<td>12.01.2006</td>
<td>1.98 (76)</td>
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<td>2.53 (103)</td>
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<table>
<thead>
<tr>
<th>Patient #5</th>
<th>Date (day.month.year)</th>
<th>FEV1 (L) (% predicted)</th>
<th>FEV1 (L) post-bronchodilator</th>
<th>FEV1/FVC (%)</th>
<th>FEF25-75 (L.s(^{-1})) (% predicted)</th>
<th>RV/TLC (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>12.09.2007</td>
<td>0.59 (24)</td>
<td>0.61</td>
<td>34</td>
<td>0.21 (6)</td>
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<tr>
<td></td>
<td>24.10.2007</td>
<td>2.16 (90)</td>
<td>2.20</td>
<td>78</td>
<td>2.03 (61)</td>
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<tr>
<td></td>
<td>8.08.2012</td>
<td>1.25 (54)</td>
<td>1.56 (67%)</td>
<td>61</td>
<td>0.82 (26)</td>
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<table>
<thead>
<tr>
<th>Patient #6</th>
<th>Date (day.month.year)</th>
<th>FEV1 (L) (% predicted)</th>
<th>FEV1 (L) post-bronchodilator</th>
<th>FEV1/FVC (%)</th>
<th>FEF25-75 (L.s(^{-1})) (% predicted)</th>
<th>RV/TLC (%)</th>
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<tbody>
<tr>
<td></td>
<td>6.11.1991</td>
<td>1.45 (42)</td>
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<td>51</td>
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<tr>
<td></td>
<td>19.02.1992</td>
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<td>36</td>
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<td>31.03.1992</td>
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<td>89</td>
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<td></td>
<td>6.05.1996</td>
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<td></td>
<td>7.06.2004</td>
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<td>2.71</td>
<td>68</td>
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</tr>
<tr>
<td>Date</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
<td>Value 5</td>
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</tr>
<tr>
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<td>---------</td>
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<td>22.04.2008</td>
<td>1.97</td>
<td>2.07</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(63)</td>
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<tr>
<td>9.02.2010</td>
<td>1.20</td>
<td>1.25</td>
<td>38</td>
<td>0.40</td>
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<td></td>
<td>(39)</td>
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<td>(15)</td>
<td>(154)</td>
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<td>1.74</td>
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<td>1.03</td>
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<tr>
<td></td>
<td>(58)</td>
<td>(58)</td>
<td></td>
<td>(30)</td>
<td>(124)</td>
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</table>

Values in italics are percentages of predicted values. FEF$_{25-75}$, forced expiratory flow between 25 and 75% of FVC; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.
Table 3. HRCT imaging features

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Date (month.year)</th>
<th>Direct signs of bronchiolitis</th>
<th>Indirect features of bronchiolitis</th>
<th>Bronchial features</th>
<th>Other imaging features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #1</td>
<td>10.2011</td>
<td>++</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Patient #2</td>
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<td>++</td>
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<tr>
<td>Patient #3</td>
<td>05.2009 10.2009</td>
<td>+</td>
<td>++</td>
<td>-</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient #4</td>
<td>01.2006</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Patient #5</td>
<td>09.2007</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Patient #6</td>
<td>02.2010</td>
<td>+</td>
<td>-</td>
<td>++</td>
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</tr>
</tbody>
</table>

1 Poorly-defined ground glass attenuation
2 V-shaped or Y-shaped

The density of abnormal findings was rated as mild (+), moderate (++), or severe (+++).

N/A, not available
**Figure legends**

**Figure 1.** HRCT of the chest in patient #1, demonstrating tree-in-bud pattern and centrilobular nodules in right (A) and left (B) lungs.
Figure 2. Fiberoptic bronchoscopy in patient #2, showing white mucosal granulations of the tracheal mucosa. A similar pattern was observed in patient #3, corresponding histiopathologically to ulcerated tracheal and bronchial mucosa with areas of necrosis and prominent eosinophilic inflammation.

Figure 3. HRCT of the chest in patient #3, demonstrating direct signs of bronchiolitis (centrilobular nodules, branching opacities, tree-in-bud pattern, bronchiolectasis) (A), and mucus plugging with “finger-in-glove” pattern (B, C).
Figure 4. Histopathological analysis of lung biopsy specimen in patient #6, demonstrating hypereosinophilic bronchiolitis, with eosinophil-rich infiltrates of the submucosa (white arrows), and accumulation (plugging) of inflammatory cells with abundant eosinophils (blue arrows) in the bronchiolar lumen (Panel A, x40; Panel B, x 20; hemalun eosine saffron).
References


