Eosinophilia and wheeze: thinking beyond asthma

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Shareable abstract (@ERSpublications)
Primary idiopathic hypereosinophilic syndrome is a rare condition that can cause end-organ damage in multiple systems. The advent of targeted monoclonal antibodies, such as mepolizumab, provides a safe and effective steroid-sparing treatment. https://bit.ly/4bgDP1u

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A previously well, 9-year-old girl was referred to the Paediatric Asthma Clinic with a 12-month history of cough, dyspnoea, and reduced exercise tolerance. She initially presented with episodic cough and wheeze which responded to asthma treatment. This progressed to acute exacerbations every 6–8 weeks characterised by increased productive cough and tachypnoea, with a baseline of exertional dyspnoea and intermittent moist cough between episodes. Treatment with daily inhaled corticosteroid (ICS) and as-needed short-acting β-agonist (SABA) did not provide significant relief. Her symptoms improved with intermittent courses of oral systemic corticosteroid treatment; however, symptoms recurred following cessation.

She had no symptoms suspicious for aspiration, atypical infections, connective tissue disease or B symptoms (fever, night sweats or weight loss). Family history was significant for paternal allergic rhinitis, and a maternal grandmother with sarcoidosis.

Examination was unremarkable with normal growth and no hypoxaemia. There were no other significant findings on examination, including no hepatosplenomegaly or adenopathy noted.

Initially, spirometry showed severe obstructive lung disease with a mixed component: forced expiratory volume in 1 s (FEV_1) 0.62 L (38% predicted) and forced vital capacity (FVC) 0.96 L (51% predicted), with FEV_1/FVC of 63% (normal 78–90%). There was a significant bronchodilator response (23%). This was presumed to be a predominantly obstructive picture with gas trapping, although further specialised testing with plethysmography was not performed. Bronchial provocation testing was not appropriate given the low volumes and exhaled nitric oxide fraction was not measured. Subsequent serial spirometry showed persistent obstruction without a bronchodilator response. Chest radiography showed hilar prominence and thickening of the right paratracheal stripe consistent with lymph node enlargement.

The patient was increased to a high-dose ICS/long-acting β-agonist combination, and further investigation was organised.

Task 1

Which feature(s) of this presentation are not consistent with asthma alone? Choose all that apply.
a) 12-month history
b) Moist, productive cough
c) Lack of response to treatment with SABA
d) Severity of obstructive lung disease
e) Response to systemic steroids

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The patient continued to have regular symptoms despite treatment with regular high-dose fluticasone/salmeterol 250/25 µg 2 puffs twice daily. Her administration technique was assessed and found to be adequate, and there were no concerns regarding compliance to treatment. To evaluate for an alternate diagnosis, such as bronchiectasis, she underwent chest computed tomography (CT). This demonstrated mild bronchiectasis, gas trapping and prominent hilar lymph nodes (figure 1). Initial investigations for causes of bronchiectasis were normal, with normal blood lymphocyte subsets, naïve T-cells, immunoglobulins, memory B-cells, vaccine responses and sweat chloride. She had a mildly elevated IgE of 223 $kU \cdot L^{-1}$ and significant eosinophilia (eosinophil count: 3.4×10^9 per L). She continued to have severe obstruction on spirometry, without a significant bronchodilator response.

To manage bronchiectasis with chronic cough and persistently low FEV_1, she was commenced on empirical treatment of 10 days intravenous piperacillin–tazobactam and regular twice a day chest physiotherapy for airway clearance. Sputum culture grew upper respiratory tract flora with 3+ leukocytes on microscopy, and piperacillin–tazobactam is the empiric antibiotic used for patients with bronchiectasis without a known pathogen at our centre. She had a limited clinical or lung function response on day 7 of treatment. Due to her previous bronchodilator response and subjective improvement with oral steroids, she was treated with 3 days of prednisolone 1 $mg \cdot kg^{-1}$ twice a day with a good response. FEV_1 improved significantly to 89% predicted. This was consistent with her previous pattern of subjective improvement with systemic steroids, although not sustained when weaned or ceased (figure 2).

Task 2

Which additional investigations are appropriate next steps to clarify the diagnosis? Choose all that apply.

a) Lower airway sampling
b) Repeat imaging
c) Sleep study
d) Antineutrophil cytoplasmic antibodies (ANCA) serology
e) Mediastinal lymph node biopsy

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The patient had a good response to oral steroids; however, this was not sustained. She was again treated with intravenous antibiotics and regular physiotherapy to manage the bronchiectasis. Lymphadenopathy was confirmed on repeat imaging and the patient progressed to an EBUS-guided biopsy, which demonstrated reactive lymphoid hyperplasia and no granulomas. There was no growth from BAL of bilateral lower lobes. Additional blood tests to assess for a rheumatological or inflammatory process, such as sarcoidosis or EGPA, were all within normal limits, including angiotensin converting enzyme, ANCA, antinuclear antibodies, C-reactive protein and erythrocyte sedimentation rate. Assessment for PCD with analysis of a nasal brushing sample with high-speed videography and immunofluorescence was also normal.

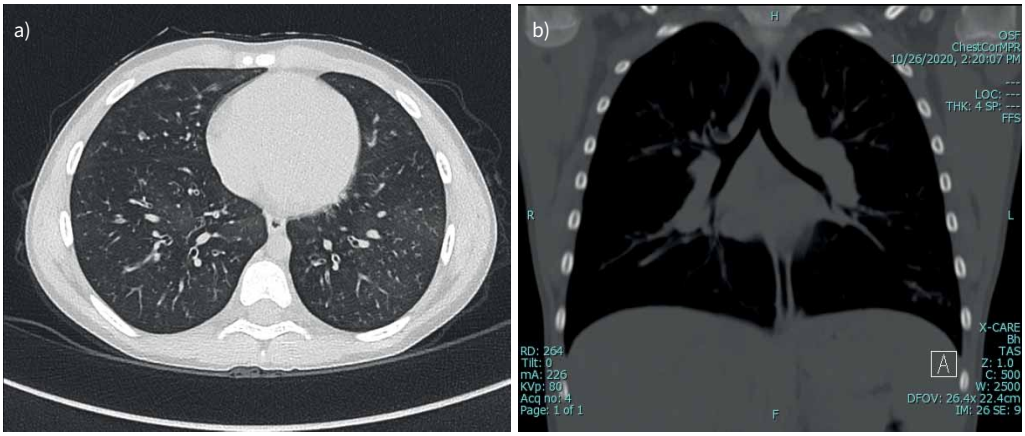

FIGURE 1 Chest computed tomography demonstrating mild bronchiectasis, gas trapping and prominent hilar lymph nodes: a) transverse plane; b) coronal plane.

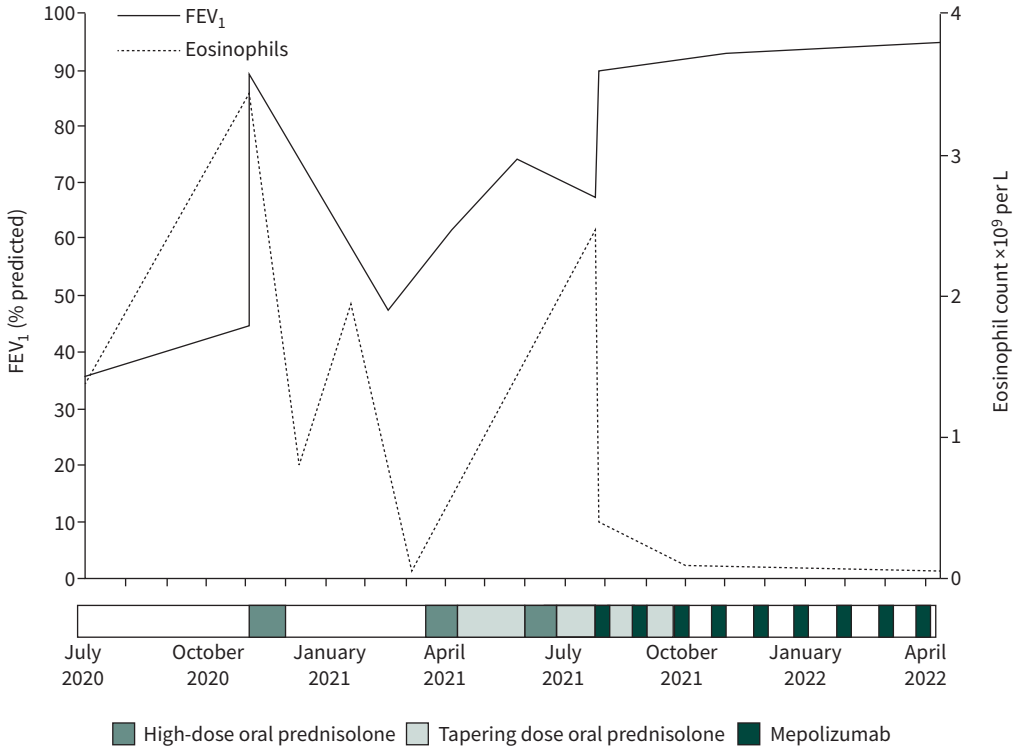

FIGURE 2 Response to steroid and mepolizumab treatment in terms of lung function and eosinophil count. FEV_1: forced expiratory volume in 1 s.

Positron emission tomography (PET)/magnetic resonance imaging (MRI) was performed due to persistent unexplained lymphadenopathy and to examine for other sites of occult disease which may help to identify a cause. The PET/MRI showed nonspecific radiopharmaceutical accumulation within hilar and mediastinal lymph nodes, prominent on MRI and not strongly suspicious of malignancy. There was mucosal thickening with low grade fluorodeoxyglucose accumulation in the paranasal sinuses, which was not supportive of a diagnosis of EGPA.

The patient recommenced systemic corticosteroids, and her FEV_1 improved to 110% predicted. Over the following 6 months she remained steroid dependent, remaining clinically well while on systemic corticosteroids but relapsing when weaned or ceased. Her eosinophil count normalised during periods of high-dose steroid treatment.

Task 3

What is the most appropriate next step?
a) Watch and wait
b) Admit for antibiotics
c) Extended immune work-up
d) Cardiopulmonary exercise test
e) Synacthen test

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The patient underwent an extended immune work-up, including cytomegalovirus and Epstein–Barr virus IgG, immunoglobulins, neutrophil oxidative test, lymphocyte subsets, soluble CD25, natural killer cell function and perforin, all of which were normal. Further infectious causes (HIV, cryptococcal infection, *Strongyloides*, *Bartonella*) were all negative. She had a normal liver ultrasound. Microarray showed an unexpected 15q11.2 deletion, which can be associated with a variable phenotype ranging from normal to a number of developmental and neurological conditions (not displayed by the patient), but has not been associated with hypereosinophilia [6].

Bone marrow aspirate (BMA) showed a mildly hypocellular marrow with normal trilineage haematopoiesis. There was eosinophilia accounting for 12% of cells with mild histiocytosis (normal <2.5%) [7]. There were no significant dysplasia/blasts. Fluorescence *in situ* hybridisation for FIP1L1-PDGFRA, a gene associated with the myeloproliferative variant of HES, was negative.

To assess for hypereosinophila in the lung as well as peripherally, flow cytometry was performed on BAL and blood samples collected at the time of bronchoscopy. Eosinophils were the most abundant population detected in BAL, comprising 43.17% of immune cells, followed by neutrophils (29.61%) and macrophages (4.38%) (figure 3a). While validated normative ranges for paediatric BAL do not exist, the presence of >40% eosinophils is clearly abnormal, with previous work showing they are usually <1% of BAL [8–10]. A similar eosinophilia was also observed in peripheral blood, with eosinophils comprising 12.83% of immune cells in whole blood samples, which again is markedly elevated (usually <1%) (figure 3b) [8].

Cytokines were measured in BAL cell-free fluid collected at the time of bronchoscopy using a multiplex assay. These tests were undertaken as part of an institutional review board approved study (Royal Children's Hospital Melbourne, HREC #25054) with informed consent provided by the patient's mother. Levels of type-2 related cytokines interleukin (IL)-4, IL-5 and IL-13 in BAL were 1.04 $pg \cdot mL^{-1}$, 55.41 $pg \cdot mL^{-1}$, and 0.82 $pg \cdot mL^{-1}$, respectively (figure 3c). These levels were 7.17-fold, 4.4-fold and 1.35-fold higher than those observed in BAL samples from healthy children (the authors' unpublished data), respectively, and identified that treatments which target eosinophils and type 2 inflammation may be helpful for the patient.

Task 4

What is the most likely diagnosis?
a) EGPA
b) Primary HES
c) PID
d) Lymphoma
e) Further investigations are required

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Based on the confirmation of lung hypereosinophilia, and the absence of an alternate cause, the patient was diagnosed with idiopathic HES.

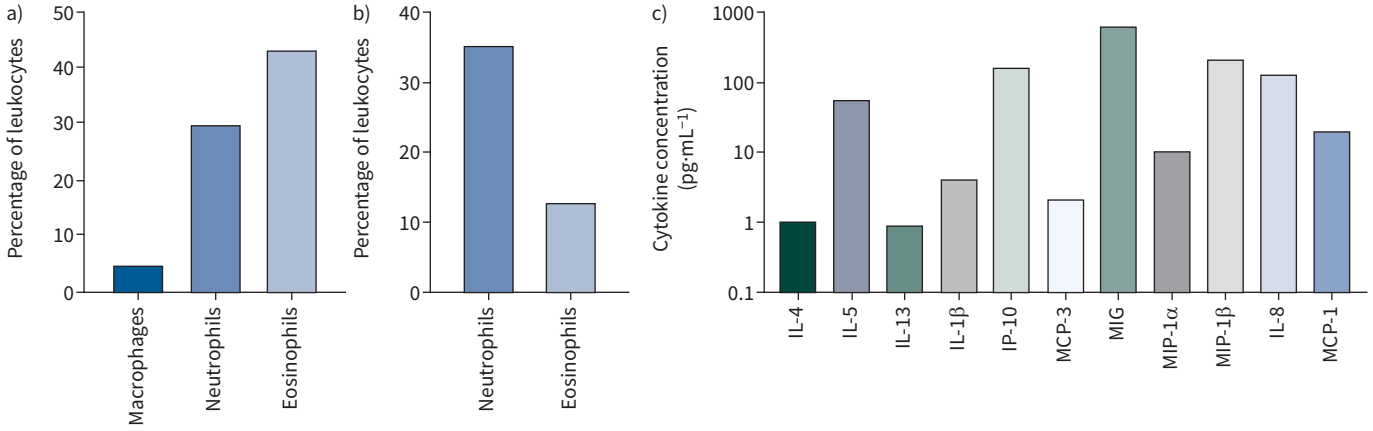

FIGURE 3 Cellular and cytokine analysis of patient samples. a) Proportions of macrophages, neutrophils, eosinophils in bronchoalveolar lavage (BAL) samples as determined by flow cytometry. b) Proportions of neutrophils and eosinophils in whole blood samples as determined by flow cytometry. c) Levels of interleukin (IL)-4, IL-5, IL-13, IL-1β, interferon-γ-induced protein (IP)-10, monocyte chemotactic protein (MCP)-3, monokine induced by gamma (MIG), macrophage inflammatory protein (MIP)-1α, MIP-1β, IL-8 and MCP-1 in BAL cell-free fluid as determined by multiplex assay (Bio-Plex; Bio-Rad Laboratories, Inc.).

The patient was commenced on the steroid-sparing agent mepolizumab (300 mg every 4 weeks by subcutaneous injection), which has been shown to be safe in primary school-age children [14], and was funded by our hospital. There was an excellent response. She weaned and ceased steroids. She is now over 6 months post-ceasing steroids with no acute exacerbations since commencing mepolizumab. Her lung function has normalised with a FEV_1 95% predicted and FEV_1/FVC of 83%. She has excellent exercise tolerance, and recently completed a triathlon. She will continue mepolizumab for 12 months before trying to wean.

Discussion

Recurrent cough and wheeze is a common presentation in the paediatric respiratory clinic. While the most common cause of this is asthma, it is important to consider alternative diagnoses particularly in difficult-to-treat cases [2, 4]. While severe asthma can lead to bronchiectasis, this is not typical and significant CT abnormalities in the presence of symptoms of wet cough should prompt consideration of other disease processes [15, 16]. The significant peripheral eosinophilia in this case was also unusual for bronchiectasis, as most bronchiectasis is driven by neutrophilic inflammation [5, 17].

Idiopathic HES is rare, particularly in children [11]. It is characterised by otherwise unexplained persistent eosinophilia for >6 months, resulting in end-organ dysfunction [11, 12]. Presentations vary, and high eosinophil levels can affect multiple systems including the pulmonary, dermatological, cardiovascular, gastrointestinal and nervous systems [11, 12], although in this case it was limited to the lungs and bone marrow. Overlap with asthma is common, with Dulohery *et al.* [18] describing 27% patients in their cohort with co-existing asthma. Bronchiectasis is not typically a feature of HES, and is generally associated more with neutrophilic inflammation. However, there is emerging evidence in adult patients with bronchiectasis that a significant sub-group have eosinophilic asthma [19, 20].

Some variants are responsive to tyrosine kinase inhibitors, while others respond to treatment with immunosuppressive agents such as corticosteroids or other immunosuppressive therapy. Steroids have significant side-effects and long-term systemic steroids should be avoided. Pulse steroids with short courses of high-dose intravenous agents can be effective, and there may also be a role for steroid-sparing biologic agents such as mepolizumab or other monoclonal antibodies.

Mepolizumab is a monoclonal antibody that reduces eosinophils by inhibiting IL-5, a cytokine that was elevated this patient's BAL. It has been shown to be a safe and effective treatment for primary HES [13]. Mepolizumab has been proven to be safe down to the age of 6 years [21], and is the only biologic agent with Federal Drug Authority approval for HES.

Conclusions

This case highlights several important learning points:

- While the most common cause of recurrent wheeze and cough in children is asthma, the first step in assessing difficult-to-treat cases is to assess for alternative diagnoses.
- Differential diagnoses for bronchiectasis with lymphadenopathy include infective, malignant and inflammatory conditions, and this case outlines an approach to working through these differential diagnoses.
- We have discussed causes and investigations of suspected HES, which can present with lung disease.
- Primary idiopathic HES is a rare condition that can cause end-organ damage in multiple systems. Previously management consisted of chronic steroid therapy, with associated toxicity. The advent of targeted monoclonal antibodies, such as mepolizumab, provide a safe and effective alternate treatment for primary HES in both adults and children.

Answer 1

b, c. The most common cause of recurrent wheeze and cough in children is asthma. In this case, the initial symptoms, response to asthma therapy, and bronchodilator response are in keeping with asthma. However, the evolution of the patient's symptoms, and in particular the presence of a moist cough and fixed airway obstruction, suggests that an alternate diagnosis may also be present. Investigation and management of children with apparent severe or difficult-to-treat asthma requires a structured approach [1–3]. The first step is always confirming asthma is the correct diagnosis [3, 4]. Education is key, and correct administration technique, treating comorbid conditions, and identifying triggers and modifiable risk factors should be repeatedly assessed. Bronchodilator response is a hallmark of asthma, and while an asthma component remains likely, the lack of subsequent bronchodilator response indicates an additional or alternative diagnosis [1, 2].

<< Go to Task 1

Answer 2

a, b, d, e. Differential diagnoses for bronchiectasis with lymphadenopathy include infective, malignant and inflammatory conditions [5]. Eosinophilia could be associated with atopic diseases (such as asthma) or small vessel vasculitides (such as eosinophilic granulomatosis with polyangiitis (EGPA)). Serology can help to identify vasculitides, although only approximately a third of children with EGPA are ANCA positive and a biopsy demonstrating granuloma is frequently needed to confirm the diagnosis. Unusual presentations of congenital conditions such as cystic fibrosis (CF), immunodeficiency and primary ciliary dyskinesia (PCD) should also be considered, although the normal sweat chloride makes CF unlikely. Lower airway sampling, either with bronchoalveolar lavage (BAL) or induced sputum, could help to identify pathogens that may be exacerbating bronchiectasis as well as to assess whether eosinophilia is present in the lung. A mediastinal lymph node biopsy may be needed to confirm the underlying diagnosis by assessing for typical and atypical infections, and rheumatological and oncological diagnoses. Endobronchial ultrasound (EBUS)-guided techniques, which are commonplace in adults, could be used to minimise the morbidity of such a biopsy. Repeat imaging is helpful to ensure the lymphadenopathy has not resolved, as might be the case if it was reactive in nature, and to inform biopsy planning.

<< Go to Task 2

Answer 3

c. Steroid-dependent respiratory symptoms and persistence of peripheral blood eosinophilia for over 6 months despite chronic steroid treatment is abnormal. Pulmonary symptoms can be the initial presentation of immune dysregulation or primary immunodeficiencies (PID). PID can lead to chronic and recurrent infections, which in turn contribute to chronic inflammation, tissue damage and progression to bronchiectasis. Complications can also include interstitial lung diseases, such as granulomatous and lymphocytic interstitial lung disease (GLILD) as a complication of common variable immunodeficiency (CVID). Perforin defects may also be implicated in lung injury. The peripheral eosinophilia could be a sign of a primary hypereosinophilic syndrome (HES), and assessment for lung hypereosinophilia would be helpful. A more complete assessment of the immune system including blood tests and a bone marrow aspirate is needed.

<< Go to Task 3

Answer 4

b. The patient met the criteria for a primary HES in that she had: 1) persistent eosinophilia >1.5×10^9 per L for over 6 months, 2) lack of evidence for other parasitic or allergic cause of eosinophilia, and 3) signs of end-organ damage with lung involvement [11]. HES is rare in children, and can affect different organ systems with variable presentation. Steroids have traditionally been the first-line treatment, with newer steroid-sparing agents proposed as alternative treatment options [12, 13].

<< Go to Task 4

Conflict of interest: J. Harrison reports roles as the Board Director of Cystic Fibrosis Community Care, and as a member of the Education and Training Committee of Thoracic Society Australia and New Zealand, outside the submitted work. The remaining authors have nothing to disclose.

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