CASE REPORT

Chronic eosinophilic pneumonia with persistent decreased diffusing capacity for carbon monoxide

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SUMMARY

We report a 15-year-old girl presenting with dry cough, exertional dyspnoea, weight loss, fever and night sweats for over 1 month. Blood tests revealed hypereosinophilia, high IgE and antinuclear antibodies levels. Chest x-rays showed bilateral peripheral infiltrates mostly in the right upper lobe which was confirmed by a chest CT. Bronchoalveolar lavage showed hypercellularity with 28% of eosinophils. Idiopathic chronic eosinophilic pneumonia was confirmed after exclusion of other causes of eosinophilic pneumonia and systemic disease. The patient responded dramatically to oral corticosteroids. Oral corticotherapy was stopped after 4 months. At 8 months of follow-up, diffusing capacity for carbon monoxide (DLCO) remained moderately low (58%) with persistent mild exertional dyspnoea. Cardiopulmonary exercise testing showed muscular peripheral limitation. Even if in our patient, mild exertional dyspnoea can be partly correlated to peripheral deconditioning, DLCO should be systematically evaluated to determine follow-up studies standards, to correlate with subclinical disease, relapse risk and to codify therapeutic options.

BACKGROUND

Idiopathic chronic eosinophilic pneumonia (ICEP) is a lung disease of undetermined origin infrequently encountered in adults and exceptional in childhood. Diagnosis requires a systematic assessment to be established. We report a 15-year-old girl presenting with an eosinophilic pneumonia. After exclusion of other known causes, the diagnosis of ICEP was considered.

CASE PRESENTATION

A 15-year-old girl was admitted to a local hospital presented with dry cough for over 1 month and persistent fever, night sweats and exertional dyspnoea for 2 weeks. Her general practitioner consulted 1 month earlier had prescribed short-course oral corticosteroid therapy. Blood testing performed 13 days later revealed an absolute eosinophilic count at $0.88 \times 10^9/l$ and serum IgE increased at 998 UI/ml. Pulmonary function tests showed a combined respiratory defect with restrictive pattern and peripheral obstructive pattern reversible following β_2 -mimetic challenge (table 1). The chest x-ray showed bilateral peripheral alveolar infiltrates which predominated in the right upper lobe. The chest CT confirmed peripheral consolidation mainly of the right upper lobe (figure 1C). She was referred to the local hospital.

She was born in France and never travelled abroad. She was exposed to animals with many pigeons on her roof, horse-riding practice and a stone-marten at home. She had no history of asthma or allergy and denied any familial or personal exposure to tobacco. She had taken no medication during the months before the disease occurred and denied any drug abuse. Biological assessment showed an inflammatory picture with a C reactive protein at 73 mg/l, blood hypereosinophilia rising to $2.2 \times 10^9/l$ and elevated IgE (998 UI/ml).

She was therefore referred to our paediatric respiratory department. On admission, her weight was 43 kg, height 161 cm, temperature was 38.6°C, pulse rate was 119/min and oxygen saturation was 100% in room air. She had lost 2 kg in 2 months. She had decreased breath sounds on the right apex, the rest of the physical examination being normal.

INVESTIGATIONS

Blood tests confirmed hypereosinophilia reaching $4600/mm^3$. Bronchoalveolar lavage (BAL) analysis revealed $1800\text{ cells}/mm^3$ with a differential count of 28% eosinophils, 53% macrophages, 17% lymphocytes and 2% neutrophils, confirming the eosinophilic pneumonia. There was no evidence of fungal, bacterial or viral infection in BAL and blood tests. Parasitological assessment was negative. The quantiferon-TB Gold test and tuberculin skin test were negative. Aspergillus precipitins, and avian's lung serologies were negative. Antinuclear antibodies were positive at 1/1280 dilution with a homogeneous pattern, but no specificity (notably negative antisyntetase antibodies) and antineutrophil cytoplasmic antibody were negative. Blood T-cell expression profile was also normal.

During the hospitalisation, her clinical condition deteriorated with weight loss (2.7 kg in 10 days), asthenia, high night fever, hard cough and orthopnea. ECG was normal. Chest x-ray worsened to a suggestive aspect of photographic negative of pulmonary oedema (figure 1A). Abdominal ultrasounds revealed a mild homogeneous splenomegaly. To rule out neoplasia a bone marrow biopsy was carried out which revealed hypereosinophilia without blast cells and a positron emission tomography (PET) scan which showed areas of hypermetabolic lung hyperactivity within lung consolidations and mediastinal and cervical nodes, spleen and bone marrow lighting-up with less intensity (figure 1D).

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Table 1 Diffusion, spirometric and biological parameters evolution during individual follow-up

	One month prior diagnosis	One month prior diagnosis post- β 2	Four days post-CS onset	Four days post-CS onset post- β 2	Month 1	Month 2	Month 5	Month 8
AV (% pred)	Na	Na	61	Na	97	89	88	93
DLCO (adj % pred)	Na	Na	42	Na	75	62	56	58
KCO (adj % pred)	Na	Na	69	Na	77	69	64	63
TLC (% pred)	Na	Na	68	Na	94	94	84	94
FVC (% pred)	48	49	51	63	89	96	97	102
FEV ₁ (% pred)	55	58	49	65	89	101	102	101
FEV ₁ /FVC (%)	98	100	90.5	97.1	95.54	99.11	98.81	94.44
FEF 25–75 (% pred)	53	70	69	93	114	149	139	146
Eosinophils ($\times 10^9/l$)	1.5	1.5	0.3	0.3	0.2	0.3	0.4	0.3
Corticosteroids (mg/kg/day)	None	None	1	1	1	1	None	None

Adj, value adjusted for haemoglobin level; AV, alveolar volume; CS, corticosteroids; DLCO, diffusing capacity for carbon monoxide or transfer factor; eosinophils, blood eosinophil count; FEF 25–75, forced mid-expiratory flow; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; KCO, DLCO/VA or transfer coefficient; Na, not available; % pred, percentage of predicted value; post- β 2, post- β 2-mimetic: 200 μ g of salbutamol; TLC, total lung capacity. Bold face, abnormal values.

Figure 1 Chest x-rays, CT scan and positron emission tomography (PET) scan follow-up chest x-rays (a) at diagnosis showing bilateral peripheral infiltrates, (b) 6 days after the onset of oral corticosteroids. High-resolution chest CT scan (c) at diagnosis showing ground-glass and alveolar infiltrates especially in the right upper lobe and with peripheral predominance in the left upper lobe; (d) PET scan showing intense hypermetabolic activity of the consolidations. (e) High-resolution chest CT scan 1 month after the onset of oral corticosteroids.

TREATMENT

We conclude to an ICEP and the patient underwent a course of oral corticosteroids (prednisolone 1 mg/kg/day).

OUTCOME AND FOLLOW-UP

Dyspnoea, fever and blood hypereosinophilia resolved within 4 days, and chest x-rays normalised in 6 days (figure 1B). Lung function tests at the beginning of the treatment showed a restrictive lung disease and impairment of diffusing capacity (diffusing capacity for carbon monoxide or transfer factor (DLCO) and transfer coefficient (KCO); table 1). After 1 month of corticosteroids a complete functional recovery was observed (table 1), blood eosinophil count was 200/mm³ and CT cleared (figure 1E). Prednisolone treatment was tapered off and weaned within 4 months.

With 10 months of follow-up she had no relapse, but complained about mild persistent exertional dyspnoea. Spirometric longitudinal assessment showed after a near normalisation at 1 month of treatment a progressive alteration of DLCO and KCO (table 1) with no obstructive or restrictive syndrome. The new CT scan was unchanged, and a repeated BAL revealed no eosinophilia. The clinical exercise test showed a limitation of aerobic metabolism with impaired oxygen uptake without limitation of ventilation. At peak exercise the oxygen alveoloarterial gradient was increased. The absence of cardiac involvement, confirmed by echocardiography suggested that the dyspnoea was secondary to a 'peripheral' muscular abnormality (muscular deconditioning and/or steroid myopathy) and an abnormal pulmonary exchanger.

DISCUSSION

ICEP is infrequent in adults and extremely rare in childhood. Described by Carrington *et al* in 1969, ICEP has been first described in childhood in 1975 in a 1-year-old infant.¹ To date, only 10 paediatric observations have been reported in the literature with no follow-up studies or series.^{1–8} ICEP belongs to the group of eosinophilic pneumonias divided in: diseases of known causes (mainly parasitic infections, allergic bronchopulmonary aspergillosis, drug reactions but also other infections and neoplasia) and of unknown causes (Churg and Strauss, idiopathic hypereosinophilic syndrome, ICEP). Diagnostic criteria for ICEP includes respiratory symptoms present for >2–4 weeks, eosinophilia at BAL greater than 25% and preferably greater than 40% (or peripheral blood eosinophilia over 10⁹ cells/l), diffuse alveolar consolidation with peripheral predominance and absence of other causes of eosinophilic pneumonia.⁹ Clinical examination is non-specific. Lung biopsy, no longer required for diagnosis, shows eosinophilic infiltration of the lung structures. The diagnosis is often delayed owing to the progressive development of symptoms and the need of a comprehensive assessment to eliminate differential diagnosis.

Aetiology remains unknown and physiopathology unclear. High level of IgE presented by this patient is frequently reported and could correspond to a non-specific rather than an antigen-driven IgE production related to T-helper (Th) type 2 cells development triggered by eosinophils activation.¹⁰ This activation is reflected by the results of the PET scan. Nosological boundaries with asthma have been previously discussed by Marchand *et al*¹¹ with on one hand: (1) 50% of adults with a diagnosis of asthma prior to that of ICEP (median time interval 42 months) and 13% developing asthma after the diagnosis and on the other hand (2) hypereosinophilic asthma that can represent a differential diagnosis. Positive antinuclear antibodies have been described in 4.4% of adults patient with mild titres.¹² The strikingly high level in our patient

was not related to a systemic disease as no other clinical sign was reported and as no specificity of these antibodies was found positive and could be as for IgE levels a non-specific marker of a global immunological disorder implying T cells. Recently, clonal TCR- γ rearrangements have been detected in 11% of adult patients (1/9) in a small sample size study and may participate within the pathogenesis of eosinophilia.¹³

ICEP is highly responsive to oral corticosteroid treatment and the preceding short course prescribed by the general practitioner has certainly lessened the initial eosinophilic count. Optimal duration is not established but usual courses of 6–12 months are prescribed. A short regimen of 6 weeks actually used on adults by GERMO'P should be of great interest in the paediatric setting with notable reduction of side effects on growth. Development of new immunosuppressive drugs like mepolizumab could also be of great interest, especially in patients with clonal expansion of T cells.¹³ Omalizumab has been moreover recently used successfully in a relapsing context in an adult. Follow-up in adults underlies risk of relapse (up to 50%), asthma development (13%). No data have been published on DLCO and KCO follow-up, its significance in relation to sub-clinical disease activity and early prognosis of relapse risk. ICEP is a disease where eosinophilic infiltration of the interstitium and pulmonary vessels is involved as well as alveolar infiltration. Decreased DLCO and KCO with normal VA may reflect a compromised pulmonary capillary volume as well as a thickening of the alveolocapillary interstitium without alveolar destruction linked to a subclinical disease. Treatment management in case of persistent moderate decreased DLCO/KCO (as presented by our patient) is not codified. In this patient exertional dyspnoea is mainly linked to peripheral muscular abnormalities, but the exact contribution of lung efficacy is difficult to appreciate.

Learning points

- In conclusion, idiopathic chronic eosinophilic pneumonia (ICEP) remains an exceptional disease in childhood with still an unclear physiopathology. Emerging new drugs have been used successfully in relapsing context in adults and their use should be evaluated in paediatric setting compared with corticosteroid and their side effects on growth. Diffusing capacity for carbon monoxide and transfer coefficient measurement should be systematically included in the functional follow-up of ICEP to assess their clinical usefulness in the long-term management of these patients.

Competing interests None.

Patient consent Obtained.

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