CASE REPORT

Chronic alveolar haemorrhage in a paediatric patient: a diagnostic and treatment challenge

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Accepted 28 March 2015

SUMMARY

Pulmonary haemosiderosis is characterised by chronic alveolar haemorrhage, which can lead to serious cardiorespiratory complications. Although considered idiopathic in most patients, there are many possible aetiologies. We present a case of an 18-year-old woman with pulmonary haemosiderosis since 4 years of age, with an inconclusive initial study, who was treated with systemic corticosteroids and hydroxychloroquine until the age of 12 years, and azathioprine since then. Multiple exacerbations led to interstitial lung disease with restrictive functional pattern. Unilateral cochlear deafness was diagnosed at the age of 12 years and occasional polyarthralgias were recorded. When she was 16 years of age the study revealed an atypical myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) pattern. Cyclophosphamide and rituximab were administered with resolution of respiratory insufficiency and functional disability, without new episodes of alveolar haemorrhage. This case of chronic pulmonary haemorrhage was revealed to be an ANCA vasculitis, the diagnosis of which was possible only after 12 years of symptoms, with clinical and functional improvement with the association of cyclophosphamide and rituximab.

results of rituximab in ANCA-vasculitis^{4 5} may change the prognosis of these patients.

CASE PRESENTATION

A previously healthy 4-year-old girl, with a mother with antiphospholipid syndrome, presented with haemoptysis and severe anaemia (lowest haemoglobin value: 4.4 g/dL). Chest X-ray revealed bilateral alveolar opacity and a bronchoscopy showed a swollen, hyperaemic and friable bronchial mucosa with haemosiderin-laden macrophages in the bronchoalveolar lavage fluid. The initial aetiological evaluation was negative, including cardiac evaluation, coagulation test, tuberculin test, sputum culture, serum serology for common viruses and immunological blood tests (antibasal glomerular membrane antibodies, coeliac disease screening, specific IgE for cow's milk proteins, ANCA, antineutrophil and antiphospholipid antibodies). Considering the diagnosis of idiopathic pulmonary haemosiderosis, the patient was started on hydroxychloroquine and systemic corticosteroids. There were multiple exacerbations (figure 1) and an almost constant need of systemic corticosteroids (increasing doses in acute exacerbations with subsequent tapering) and sporadic blood transfusion. At the age of 12 years, she was diagnosed with unilateral cochlear deafness, interpreted as a medication side-effect after otorhinolaryngology investigation. Hydroxychloroquine was replaced by azathioprine (in view of the corticoid sparing effect), without major improvement. Thoracic CT scan showed ground glass pattern and air-trapping areas in the lower 2/3 of the lungs (figure 2), with restrictive functional pattern and progression to nocturnal and exertional hypoxaemia. The patient had multiple infections (predominantly respiratory) and adverse systemic corticosteroids effects (Cushing syndrome and osteoporosis). Open-lung biopsy was performed at 14 years of age, and showed extensive recent and prior alveolar haemorrhage, multifocal septal thickening, non-specific inflammatory infiltrate and destruction and disruption of elastic fibres, without identification of granulomatous lesions or vasculitis/capillaritis; immunohistochemical study was normal. By the age of 16 years, the patient had occasional non-specific polyarthralgias. She remained without renal, mucocutaneous or gastrointestinal manifestations. At this age, the repetition of the immunological blood tests detected an elevation of the c-ANCA titre (1/640) with atypical pattern and positive antimyeloperoxidase (MPO; 101 U/mL) leading to the diagnosis of MPO-AAV. The pulmonary involvement caused

BACKGROUND

Pulmonary haemosiderosis is a rare disease characterised by chronic alveolar haemorrhage and a heterogeneous clinical course, ranging from remission with first-line treatment to progression to cardiorespiratory failure. Although pulmonary haemosiderosis is often idiopathic in children, it can be caused by a broad group of diseases. Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a necrotising pauci-immune vasculitis of small and medium vessels, affecting predominantly renal and pulmonary vasculature. It includes granulomatosis with polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis and eosinophilic granulomatosis, polyangiitis (formerly Churg-Strauss vasculitis) and single-organ AAV.¹ Diagnosis can be challenging due to clinical heterogeneity and low incidence, mainly at paediatric age. Untreated AAV has a high mortality rate, and corticosteroids and cyclophosphamide greatly improved the prognosis. Other drugs are needed to induce remission, and to prevent relapse and organ damage secondary to both disease and therapy.² Rituximab is a monoclonal anti-CD20 antibody causing B-cell depletion. These cells participate in ANCA-vasculitis pathogenesis and are associated with the disease activity.³ The promising

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To cite: Freitas A, Senra V, Marinho A, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-206856

Figure 1 Haemoglobin value evolution illustrating the multiple disease exacerbations.

severe dyspnoea on minimal exertion, and orthopnoea with supplemental oxygen need of up to 2.5 L/min, in spite of corticosteroid 15 mg/day, which led to starting rituximab (375 mg/m² intravenous weekly for 4 weeks) with 2 initial doses of cyclophosphamide (10 mg/kg intravenous). Rituximab was repeated in 6 months when B-cell repopulation occurred. After 8 months of treatment, the patient was asymptomatic (without dyspnoea, orthopnoea or haemoptysis, with no supplementary oxygen required and with no severe respiratory infections); prednisolone (5 mg/day) was given at weaning and there was no cytopaenia. There was also an increase in haemoglobin (Hb; 10.4 g/dL to 11.7 g/dL), and an improved 6 min test (an increase in distance from 62% to 83% of the expected with minimum peripheral oxygen saturation, which increased from 77% to 84%) and respiratory function (10% increase in vital functional capacity from 58 to 68%, but keeping the restrictive ventilatory pattern). The patient maintained the radiological pattern described earlier in the thoracic CT. The last analytical control revealed Hb 13.6 g/dL, ANCA 1/160 and MPO 21 UQ. Today, the patient is 21 years old, has a normal daily life and social activities and is completing her graduation at nursing school.

DISCUSSION

AAV is a rare disease in children. The most common AAV at paediatric age is granulomatosis with polyangiitis (GPA), which has an estimated incidence of 0.64 per 100 000 per year.⁶ Rare paediatric studies and absence in diagnostic criteria validated for paediatric patients makes the medical approach particularly challenging.⁷ In patients with pulmonary haemosiderosis

without response to first-line treatment, secondary aetiology must be suspected. Clinical and laboratory surveillance should be maintained in these cases. In the paediatric patient described, MPO-AAV diagnosis was possible only after 12 years of severe symptoms.

The clinical features do not fulfil the EULAR/PRINTO/PReS criteria⁸ for GPA (box 1), but they lack sensitivity and specificity.^{9 10} There are no defined diagnostic criteria for microscopic polyangiitis (MPA), and this disease is even rarer in paediatric patients. The difficult distinction between GPA and MPA has led to the frequent grouping of patients as AAV.

AAV multiorgan involvement and morbidity, secondary to the disease and treatment, demand new immunosuppressive therapies. Rituximab is a new therapeutic options, inducing remission with efficacy similar to that of cyclophosphamide in RAVE⁴ and RITUXVAS,⁵ in clinical trials. The RAVE trial shows rituximab as being better at preventing relapse and in severe disease. Some authors use a rituximab and cyclophosphamide combination in severe cases to reduce cyclophosphamide cumulative doses and their side effects.^{11 12} Our patient had a severe clinical course and rituximab and cyclophosphamide-induced remission, with good functional results. Rituximab was repeated when there was B-cell repopulation. This approach, also described in other trials, is based on the observation of increasing B cells count and ANCA title before clinical relapse.^{12 13} Few paediatric case reports describing rituximab efficiency in AAV are published and there is one paediatric case report of AAV with pulmonary involvement in which cyclophosphamide and rituximab were effective in inducing remission.^{14 15}

We described a teenaged patient with MPO-ANCA-associated vasculitis with severe pulmonary involvement, whose diagnosis

Figure 2 Thoracic CT scan showing ground glass pattern and air-trapping areas in the lower 2/3 of the lungs.

Box 1 Granulomatosis with polyangiitis (GPA)—EULAR/PRINTO/PReS criteria⁸

At least three of the six following criteria:

- ▶ Histopathology
- ▶ Upper airway involvement
- ▶ Laryngotracheobronchial stenoses
- ▶ Pulmonary involvement
- ▶ ANCA positivity
- ▶ Renal involvement

was only possible after 12 years of symptoms, and with symptomatic and functional improvement after rituximab and cyclophosphamide treatment.

Learning points

- ▶ Pulmonary vasculitis can be the cause of pulmonary haemosiderosis and it is a challenging diagnosis due to its multiple forms and rarity, particularly in paediatric patients.
- ▶ Patients with atypical or severe progression should be reassessed regularly to achieve proper diagnosis and treatment because it can improve prognosis.
- ▶ Rituximab might be an effective therapeutic approach in paediatric patients with pulmonary antineutrophil cytoplasmic antibodies-associated vasculitis.

Acknowledgements Joana Correia (Centro Hospitalar do Porto—Pediatrics) and Teresa Sequeira (Centro Hospitalar do Porto—Medicine) made substantial contributions to the acquisition, analysis, or interpretation of clinical data.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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