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CASE REPORT

Bronchoalveolar lavage findings in a young adult with idiopathic pulmonary haemosiderosis and coeliac disease

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Bronchoalveolar lavage findings in a young adult with idiopathic pulmonary haemosiderosis and coeliac disease. D. Bouros, P. Panagou, T. Rokkas, N.M. Siafakas. ©ERS Journals Ltd 1994.

ABSTRACT: Idiopathic pulmonary haemosiderosis is a rare disease of unknown autoimmune aetiology, mainly affecting children and adolescents. A variety of coexisting autoimmune diseases have been described, including coeliac disease.

We describe the case of a man, aged 19 yrs, presenting with a one year history of recurrent haemoptysis. Gluten and gliadin antibodies were positive, and the jejunal biopsy revealed villous atrophy consistent with the diagnosis of coeliac disease. Bronchoalveolar lavage fluid analysis showed a mean haemosiderin score (Golde index) of 240, and a local suppressor/cytotoxic profile on immunocytology.

Both clinical and immunological improvement was obtained after a month of gluten-free diet. These immunological findings provide new insight into the pathogenesis of this disease.

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Idiopathic pulmonary haemosiderosis (IPH) is a rare disease of unknown aetiology, characterized by recurrent episodes of haemorrhage into the lung, haemoptysis and secondary iron deficiency anaemia, and affecting mainly children and adolescents. The disease is usually fatal [1, 2]. Only 12 cases of IPH with coeliac disease have been reported [1–9]. In three of these cases, disease onset occurred after the patient had reached 15 yrs of age [5, 6, 8]. Recently, the colorimetric blue intensity of the cytoplasm of alveolar macrophages (AMs) on iron stain (*i.e.* Perl's Prussian blue stain) has been proposed as an accurate method of quantifying the severity of pulmonary haemorrhage [10, 11]. The highest values are observed in IPH, probably due to the chronicity of the disease [12–14]. However, no comparison has been made between this and other methods, such as high resolution computerized tomography (HR-CT) or pulmonary function tests. Although the pathogenesis of the disease is believed to be of immunological origin, local immune information from bronchoalveolar lavage (BAL) and blood flow cytometric analysis is lacking in this rare combination.

Case report

A man aged 19 yrs presented with recurrent haemoptysis during the last year, increasing dyspnoea on exertion (II/IV), weight loss (6 kg in the previous two months), and anaemia. One year previously he had an episode of haemoptysis and was admitted to a local hospital, where a low haematocrit (24%) was found. He was transfused with two units of blood. A probable diagnosis of duodenal ulcer was made, but no endoscopy was performed at that time.

The patient was not taking any drug that could have provoked pulmonary haemorrhage. At examination he was pale with anaemic conjunctivae. The remaining physical examination was unremarkable, except for mild tachycardia (100 beats·min^{-1}), and vague symptomatology of flatulence. No biological signs of malabsorption were present.

Laboratory investigation showed hypochromic anaemia, with haemoglobin 71 g·l^{-1} (normal 115–155 g·l^{-1}), serum iron 5.2 µmol·l^{-1} (normal 14–32 µmol·l^{-1}), iron-binding capacity 53.7 µmol·l^{-1} (normal 45–82 µmol·l^{-1}). Serum immunoglobulins were normal. Serology for collagen vascular disease, including lupus erythematosus cells, antinuclear antibodies, rheumatoid factor, double-stranded deoxyribonucleic acid (DNA), anti-sclero 70 were all negative. Renal function parameters were negative for the presence of proteinuria, microscopic haematuria, and casts. Serum vitamin B_{12} was 133 pmol·l^{-1} (normal 150–750 pmol·l^{-1}), folic acid 75 nmol·l^{-1} (normal >4 nmol·l^{-1}, D-xylose 2.8% (normal >4.1%), human leucocyte antigen (HLA) B_8 and HLA DR_3 were positive. Gliadin and reticulin antibodies were positive. Serum immune complexes and complement C1q, C5 and C6 were slightly increased. Radioallergosorbent test (Rast) for cow's milk, eggs, cereal, fruits and vegetables were negative. No antiglomerular basement membrane antibodies were present in serum. Antinuclear anticytoplasmic antibodies were repeatedly negative. Arterial

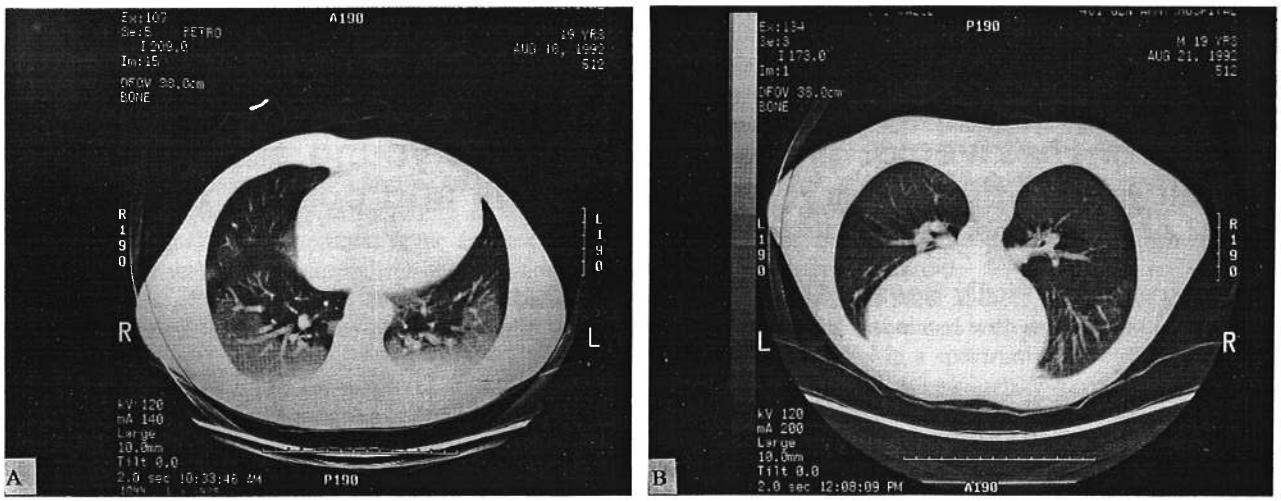

Fig. 1. – Computerized tomography of the thorax in supine (A) and prone (B) position, showing dense alveolar type opacities at lung bases with no change with body position.

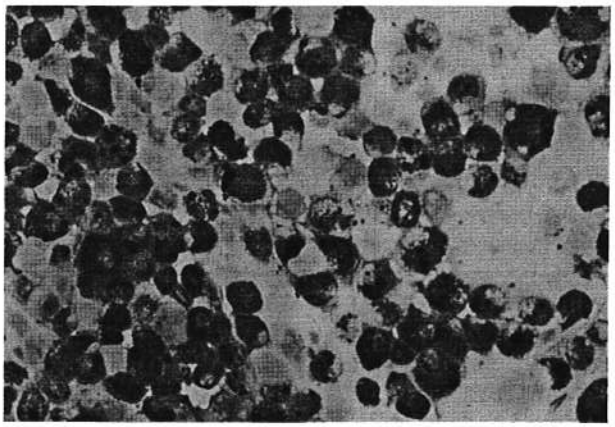

Fig. 2. – Perl's Prussian blue stain of a bronchoalveolar lavage fluid (BALF) specimen, showing the intensity of staining the cytoplasm of alveolar macrophage (Golde index of 240).

blood gases with fractional inspiratory oxygen (F_{IO_2}) 0.21, at rest were arterial oxygen tension (Pa_{O_2}) 12.8 kPa (96 mmHg), arterial carbon dioxide tension (Pa_{CO_2}) 5.12 kPa (39 mmHg), pH 7.4.

Chest radiographs (posteroanterior and lateral) were normal. Pulmonary function tests including spirometry and lung volumes were normal. Diffusion capacity of the lungs for carbon monoxide (D_{LCO}) was decreased (60% pred). Ergospirometry with an incremental protocol (30 W·3 min^{-1}) showed a decreased maximal oxygen uptake ($\dot{V}O_2max$) 1.62 $l \cdot min^{-1}$ (56% pred), a diffusion type limitation at peak exercise (120 W) and abnormal cardiac performance, ratio of heart rate (HR) increase per MET, (ΔHR/MET) 18.07, (normal 9±2 beats/MET), due to deconditioning and anaemia, and low anaerobic threshold. [MET=$\dot{V}O_2$ (exercise)/VO_2 (resting); 1 MET=3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, at rest].

Computerized tomography (CT), conventional and high-resolution (HR-CT), showed a diffuse alveolar filling pattern, especially at the lung bases posteriorly, both in prone and supine postures, with no change on altering the posture (fig. 1).

Jejunal endoscopic biopsy showed villous atrophy consistent with coeliac disease. Fibreoptic bronchoscopy was normal and bronchoalveolar lavage (BAL), performed in a subsegmental right middle lobe bronchus, showed a progressively more blood-stained bronchoalveolar lavage fluid (BALF). BALF cytological analysis showed 10.2×10^{10} cells·l^{-1}, with 90% AMs, 7% lymphocytes and 3% neutrophils. Cytological analysis revealed more than 90% haemosiderin-laden AMs. The colorimetric blue intensity of AM cytoplasm on Perl's Prussian blue stain (Golde index) was 240 (normal 4–25), (fig. 2).

BALF immunocytology with flow cytometry (FACS-star plus, Becton-Dickinson) showed 10.2×10^{10} cells·l^{-1}, AMs 87%, lymphocytes 10%, and neutrophils 3%. T-lymphocytes were 66%, B-lymphocytes 3%, and T4/T8=0.5. Blood T4/T8 ratio was found to be 1.4. Transbronchial biopsy showed mild to moderate thickening of the alveolar septa and nonspecific alveolar haemorrhage. Staining with Prussian blue showed numerous macrophages

Table 1. – Bronchoalveolar lavage findings before and one month after gluten-free diet

Gluten-free diet	Cells·ml^{-1}	AMs %	Lym %	Neut %	T-cells %	T4:T8 ratio	Golde index
Before	10.2×10^4	87	10	3	66	0.5	240
After	8.8×10^4	92	7	1	73	1.4	180

AMs: alveolar macrophages; Lym: lymphocytes; Neut: neutrophils.

full of iron pigment. No evidence of vasculitis, inflammation, granulomata or alveolar wall necrosis was found on the biopsy specimen. Immunofluorescence was negative.

The patient was given a gluten-free diet, with clinical improvement continuing for six months on follow-up. Repeated BALF analysis after one month showed a decrease in haemosiderin-laden AMs (55%) with a Golde index of 180. BALF immunocytology showed 8.8×10^{10} cell·l^{-1}, AMs 92%, lymphocytes 7%, neutrophils 1%, and T4/T8 ratio 1.4 (table 1).

Discussion

Idiopathic pulmonary heamosiderosis with coeliac disease is an extremely rare combination, of which only 12 cases have been reported [1–9]. The age of onset of symptoms was in childhood in all except four cases including our own [4, 6, 8] (table 2). Three of the 12 cases were female. The diagnosis of coeliac disease was biopsy proven (villous atrophy) in all but one patient [3]. However, an alternative approach would be to perform biopsies only in those patients who have serological evidence of coeliac disease [8]. Antibodies to reticulin and gliadin were found in patients with coeliac disease in 78 and 95% respectively [15]. Thus, a jejunal biopsy is justified in those patients with IPH and serological evidence of coeliac disease, even if the patient is free of intestinal symptoms [8]. Evidence for a causal relationship between the two diseases is lacking. However, treatment with a gluten-free diet alone, apparently, has beneficial effects, not only on the gut but also on the lung disease [1, 7]. Our patient showed a clinical and BALF analysis improvement after a gluten-free diet. BALF analysis may be used as a simple and valuable technique for follow-up of these patients on a gluten-free diet. However, caution is needed in interpreting BALF changes in our patient after only one month of gluten-free diet.

Other autoimmune disorders have been reported in patients with IPH, such as autoimmune haemolytic anaemia, monoclonal gammopathy, rheumatoid arthritis, thyrotoxicosis, microscopic polyarteritis, and hypothyroidism [16, 20].

In our patient, HR-CT showed a diffuse alveolar filling pattern at the lung bases, whilst the chest radiograph was normal. This finding has clinical significance, and suggests that every patient with unexplained recurrent haemoptysis and normal chest radiograph should be investigated with HR-CT [21]. Furthermore, fibreoptic bronchoscopy, aside from HR-CT, is necessary to investigate patients with haemoptysis and normal chest X-ray.

The low diffusion capacity found on pulmonary function test of our patient can be explained by the underlying pulmonary thickening of alveolar septa, which might be the result of repeated episodes of pulmonary haemorrhage.

Ergospirometry showed a diminished maximal aerobic power (Vo_2max), probably due to diffusion type limitation and anaemia. However, other ergospirometric data are lacking in the literature for comparison.

BALF iron stain showed a mean haemosiderin score (Golde index) of 240. In normal controls this score ranges from 4–25 [22]. High haemosiderin values are observed in IPH, probably due to chronicity of the disease [13, 14, 22]. The histological examination of the transbronchial lung biopsy specimen of our patient was consistent with the diagnosis. In addition, other aetiologies of pulmonary haemorrhage were excluded on patient's work-up.

Immunocytological analysis of BALF by flow cytometry showed a local suppressor/cytotoxic profile of T-lymphocytes, with a normal T4/T8 ratio in blood. This suggests that the BALF findings may be a response to local presence of an unknown antigen. A relationship of immunoregulation to disease activity is suggested. Conceivably, disease activity may be mediated by suppressor T-cells, since the T4/T8 ratio increased from 0.5 at the acute phase, to 1.4 at the remission phase.

This T4/T8 ratio change means that the relative amount of T8 lymphocytes decreased in lung alveoli when the patient was on the gluten-free diet and, presumably,

Table 2. – Reported cases of idiopathic pulmonary haemosiderosis with coeliac disease

Authors	[Ref]	Age at onset yrs	Sex	Coeliac disease		Treatment
				Biopsy proven	AGA	
Lane and Hamilton 1971	[1]	9	M	+	NR	Azathioprine 100 mg daily
Bailey and Groden 1979	[2]	7	M	+	NR	Azathioprine 150 mg daily
Labbe *et al.* 1980	[3]	15	M	+	NR	NR
Rieu *et al.* 1983	[4]	13	F	+	NR	Gluten-free diet
Wright *et al.* 1983	[5]	14	M	+	NR	Gluten-free diet
		9	F	+	NR	Gluten-free diet
		26	M	+	+	Gluten-free diet, prednisolone (initially)
Ludmerer and Kissame 1986	[6]	36	M	+	NR	Gluten-free diet
Reading *et al.* 1987	[7]	4.5	M	+	+	Gluten-free diet
Pacheco *et al.* 1991	[8]	22	M	+	+	Gluten-free diet
Perelman *et al.* 1992	[9]	10	F	+	-	Gluten-free diet
Present case		18	M	+	+	Gluten-free diet

+: positive; -: negative; NR: not reported; AGA: antigliadin antibody.

improved. However, since it is possible that, in the presence of abundant red cells, T-cells, particularly activated T-cells, could be lost by clumping during disease exacerbations, one must consider these data with some circumspection, until they are confirmed by additional studies.

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