
**Idiopathic pulmonary haemosiderosis and autoimmune hypothyroidism: bronchoalveolar lavage findings after cimetidine treatment**

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**Introduction**

Idiopathic pulmonary haemosiderosis (IPH) is a rare disease of unknown aetiology. Its association with other diseases may be of help in establishing its pathogenesis. A few single case reports of IPH with other concurrent autoimmune diseases, have been reported as: autoimmune haemolytic anaemia (1), monoclonal gammopathy (2), rheumatoid arthritis (five cases) (3), thyrotoxicosis (4), and recently a case of systemic vasculitis (5). However, a case of idiopathic pulmonary haemosiderosis and autoimmune hypothyroidism has never been reported. Recently, the calorimetric blue intensity of the cytoplasm of alveolar macrophages (AM) on iron stain (i.e. Perl's prussian blue stain) has been proposed as an accurate method of quantifying the severity of pulmonary haemorrhage (6–7). Furthermore, the local immune process on the alveoli has not been studied in this rare entity, as well as the effects of treatment other than corticosteroids and gluten-free diet (8).

**Case Report**

The patient was a 20-year-old male who was admitted to hospital for evaluation of known IPH, because of his enrolment in the army. Ten years previously this patient had presented with recurrent, severe episodes of haemoptyses. Investigation revealed iron deficiency anaemia, and his chest radiograph showed diffuse alveolar shadows. Bronchoscopy at that time was normal, but haemosiderin-laden AM were found on bronchial washings. Autoantibody screen was negative. At that time, other causes of pulmonary haemorrhage were excluded and a diagnosis of idiopathic pulmonary haemosiderosis was made. He was subsequently treated with a course of corticosteroids, with gradual remission of the disease. Ten years later, the patient enrolled in the army and medical examination revealed clinical findings consisting of anaemia, hypothyroidism and dermal ichthyosis. Haematology and serum biochemical analysis showed sideropenic anaemia. Indirect and direct Coombs's tests were negative. Thyroid hormones were: thyroxine 2 ng ml⁻¹ (normal range 50–120), triiodothyronine 0.2 ng ml⁻¹ (normal range 0.7–2), TSH > 30.0 μU ml⁻¹ (normal values 0.6–3.0). Anti-thyroglobulin antibodies were positive (1:400), anti-thyroid microsomal antibodies were positive (1:2560), but the antimitochondrial antibodies were negative. Technetium 99 scan showed a diffusely decreased uptake by the thyroid gland. Serum complement C3 and C4 levels and results of liver function tests were normal. Lupus erythematosus cells, anti-nuclear antibodies and rheumatoid factor were negative. Anti-neutrophil cytoplasmic antibodies and serology for collagen vascular disease were negative. Serum immune complexes were 5 μg ml⁻¹ (normal < 1.5 μg ml⁻¹). Gliadin and reticulin antibodies were negative. Anti-glomerular basement membrane antibodies were not found. A TRH test showed an excessive response to TSH. Pulmonary function tests (spirometry and lung volumes) showed a mild restrictive ventilatory defect, but the transfer factor for carbon monoxide corrected for alveolar volume (KCO) was reduced (70% of predicted value). Arterial blood gases and chest radiograph were normal.

Fibreoptic bronchoscopy revealed a normal bronchial tree, and bronchoalveolar lavage fluid (BALF) analysis performed in clinical remission showed 11.4 × 10⁴ cells ml⁻¹ with 82% AM, 16% lymphocytes and 2% neutrophils. Cytological analysis revealed 40% haemosiderin-laden AM. Colorimetric

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Table 1 Bronchoalveolar lavage findings before and after 1 month of treatment with cimetidine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cells ml⁻¹</th>
<th>AM (%)</th>
<th>Lym (%)</th>
<th>Neut (%)</th>
<th>T-cells (%)</th>
<th>CD4⁺:CD8⁺ ratio</th>
<th>Golde index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>11.4 × 10⁴</td>
<td>82</td>
<td>16</td>
<td>2</td>
<td>66</td>
<td>0.3</td>
<td>120</td>
</tr>
<tr>
<td>After</td>
<td>9.3 × 10⁴</td>
<td>89</td>
<td>10</td>
<td>1</td>
<td>73</td>
<td>1.2</td>
<td>30</td>
</tr>
</tbody>
</table>

AM, alveolar macrophages; Lym, Lymphocytes; Neut, neutrophils.

blue intensity of AM cytoplasm on Pearl’s prussian blue stain (Golde index) was 120 (normal 5–25) (9). Flow cytometry lymphocyte-phenotyping of BALF was performed with a fluorescence activated cell analyser (FACS-star plus, Becton-Dickinson, San Jose, CA, USA) used to calculate the absolute CD4⁺ and CD8⁺ cells, and the CD4⁺:CD8⁺ ratio. We used fluorescein-conjugated monoclonal antibodies OKT3, OKT4, OKT8 (Ortho diagnostics, Raritan, NJ, U.S.A.), and B1 (Coulter Immunology, Hialeah, FL, U.S.A.) and found a CD4⁺:CD8⁺ ratio: 0.30 (Table 1). Blood CD4⁺:CD8⁺ ratio was 1.32. Transbronchial biopsy showed alveolar spaces with haemosiderin-laden AM with moderate thickening of the alveolar septae and slight increase of type II cells. There was no evidence of vasculitis or granuloma formation. Using the immunofluorescence technique, no antibody or complement deposition was found on lung tissue. Sperm analysis showed findings consistent with asthenospermia. The patient was put on treatment with thyroxine 0.1 mg daily, and cimetidine 400 mg three times daily. His clinical condition in terms of anaemia, hypothyroidism and ichthyosis improved dramatically. Similarly, his asthenospermia was reversed. Repeat BALF analysis after 3 months of treatment showed: 9.3 × 10⁴ cells ml⁻¹ with 89% AM, 10% lymphocytes and 1% neutrophils. Cytological analysis revealed 10% haemosiderin-laden AM. Colorimetric blue intensity of AM cytoplasm (Golde index) was 30. Immunocytology of BALF showed a CD4⁺:CD8⁺ ratio: 1.3 (Table 1). Blood CD4⁺:CD8⁺ ratio was 1.52. After 5 years follow-up, there has been no recurrence of symptoms and the patient is symptom-free.

Discussion

This case fulfils the criteria for the diagnosis of IPH, since the patient had recurrent pulmonary haemorrhage in the absence of other explanatory conditions, such as infection, heart or systemic disease as Goodpasture’s syndrome, Wegener’s disease, or collagen vascular disease. The course of the disease was also consistent with the diagnosis of IPH, since it presented with repeated relapses and remissions over a period of more than 10 yr. In addition, consistent with the diagnosis of IPH was the histologic examination of the transbronchial lung biopsy specimen of our patient.

Autoimmune hypothyroidism was also well-documented in the patient, since despite the decreased thyroid hormones, the excess response to TRH test, and the decreased Technetium 99 uptake by the thyroid gland, the anti-thyroid microsomal antibodies and thyroglobulin antibodies were positive.

The aetiology of the disease remains unknown, but autoimmunity is strongly suspected (4). However, the autoimmune hypothesis has not been proved. No consistent immunological abnormality has been reported, and on lung biopsies no immunoglobulins, immune complexes or complement depositions are found.

This case is the first in the literature to describe such a rare combination of diseases, and outlines the possibility of a common pathogenetic mechanism between IPH and other autoimmune diseases. Previous reports suggest a link between IPH and a variety of other autoimmune diseases (1–5,8).

The patient presented with severe autoimmune hypothyroidism and asthenospermia. On treatment with thyroxine for his hypothyroidism and cimetidine for its possible immunoregulatory effects on the CD8⁺ T-lymphocytes, all the underlying diseases were ameliorated. The severe dermal ichthyosis was also cleared.

Several investigators (10–12) have described studies showing that histamine type 2 receptor antagonists, such as cimetidine, prevent the suppression of lymphocyte effector function by histamine. Direct inactivation of suppressor T-cells may account for this phenomenon, or it may be that the production of a histamine-induced suppressor factor is inhibited (11). Our findings suggest that cimetidine reduces the number of suppressor T-cells in vivo, thereby causing a reduction in functional suppressor
activity. This finding may have clinical implications changing our approach to this disease, since the best treatment is not yet known, due to lack of prospective controlled studies of such a rare disease with a variable course.

Immunocytologic analysis of BALF by flow cytometry showed a suppressor/cytotoxic profile of T-lymphocytes with a normal CD4+/CD8+ ratio in blood. These observations are of interest since they confirm our previous observations (8), and suggest 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 CD4+/CD8+ ratio increased from 0.3 before treatment, to 1.3 after treatment. This change suggests that the relative amount of CD8+ lymphocytes decreased in lung alveoli, when the patient was under treatment and presumably improved. Similarly, the Golde index reduced from 120 to 30 suggesting that occult pulmonary haemorrhage decreased after treatment. These findings give new insights into pathogenesis of the disease, and call for prospective multicentre trials for new modes of treatment including cimetidine. The relation of the local suppression to disease activity has also to be investigated. Furthermore, BALF analysis may be used as a simple and valuable technique for follow-up of these patients.

References