Eur Respir J 1997; 10: 1405–1407
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European Respiratory Journal
ISSN 0903 - 1936

CASE STUDY

Propylthiouracil-induced alveolar haemorrhage associated with antineutrophil cytoplasmic antibody

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Propylthiouracil-induced alveolar haemorrhage associated with antineutrophil cytoplasmic antibody. M. Ohtsuka, Y. Yamashita, M. Doi, S. Hasegawa. ©ERS Journals Ltd 1997.

ABSTRACT: Propylthiouracil (PTU) is known to cause vasculitis as a rare complication. We report the case of a patient who developed alveolar haemorrhage and haematuria whilst treated with PTU.

The serum was positive for antineutrophil cytoplasmic antibody (ANCA) with myeloperoxidase (MPO) specificity (MPO-ANCA). All symptoms resolved completely after discontinuation of PTU.

Alveolar haemorrhage or pulmonary-renal syndrome associated with antineutrophil cytoplasmic antibody with myeloperoxidase specificity may be a new complication of propylthiouracil therapy.

Eur Respir J 1997; 10: 1405–1407.

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Keywords: Alveolar haemorrhage, antineutrophil cytoplasmic antibody, propylthiouracil, vasculitis

Received: September 4 1996
Accepted after revision February 1 1997

Propylthiouracil (PTU) can cause a number of adverse reactions including leucopenia, rash, fever, arthritis, vasculitis and lupus-like syndrome. However, pulmonary complications, including interstitial pneumonia, cavitary lung lesions, adult respiratory distress-like syndrome and pleural effusions, are extremely rare [1, 2].

Recently, a complication of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis has been reported during PTU therapy [3–5]. STANKUS *et al*. [6] reported a case of ANCA-positive hypersensitivity vasculitis after administration of PTU, manifested as respiratory distress with diffuse pulmonary infiltrates.

We present the case of a patient who developed alveolar haemorrhage and microhaematuria whilst treated with PTU. ANCA-associated vasculitis induced by PTU might be the cause of the haemorrhage.

Case report

A 44 year old woman, who had a history of hyperthyroidism, was referred to our hospital for recurrent haemoptysis and pulmonary infiltrates in December 1991.

Her condition was diagnosed as Graves' disease with hyperthyroidism in 1987. She was initially treated with PTU (150 mg *p.o. q.d.*) for 8 months, and then underwent partial thyroidectomy. PTU therapy (50 mg *p.o. q.d.*) was reinstituted 2 years later because of relapse of hyperthyroidism. Seven months before referral, she had developed mild alopecia, photosensitivity, polyarthralgia, and polyarthritis, for which she occasionally took a nonsteroidal anti-inflammatory drug. There was no radiological abnormality on joint films.

Five weeks before admission, the patient presented at a nearby hospital with low grade fever and productive cough, with mild haemoptysis. Chest radiography revealed bilateral inhomogeneous opacities (fig. 1). She was given a 7 day course of oral antibiotics, with some improvement in her symptoms and lung infiltrates on radiography. However, the same symptoms reappeared 2 weeks later. Chest computed tomography revealed diffuse alveolar infiltrates, with fine nodules, predominantly in the right upper and the left lower lobes (fig. 2). At this time, PTU therapy was stopped. The patient has

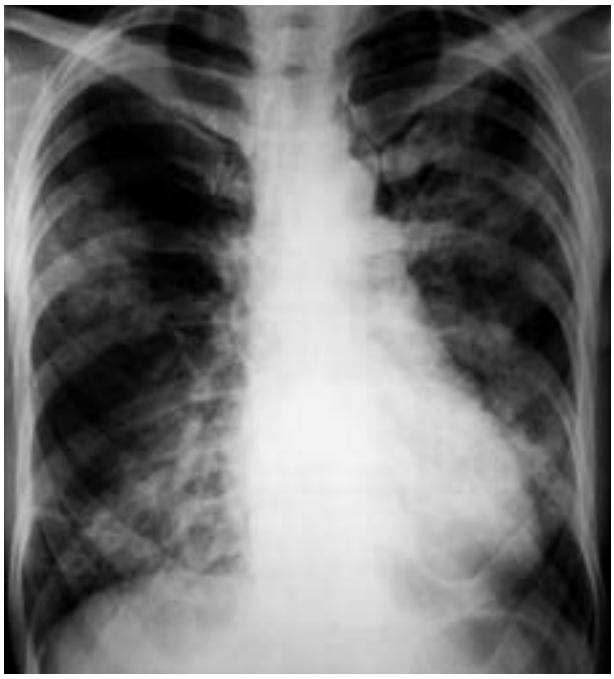

Fig. 1. – Chest radiograph showing bilateral inhomogeneous opacities.

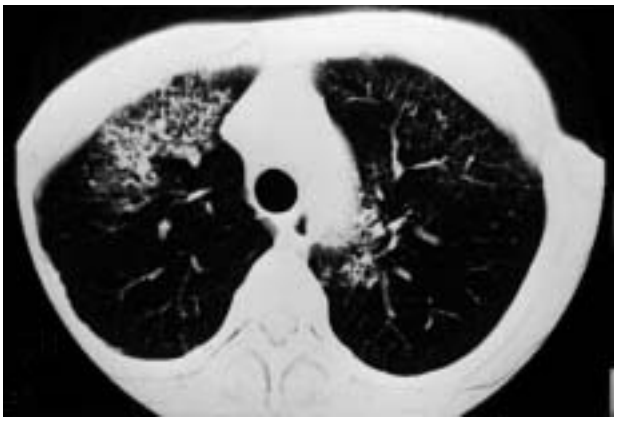

Fig. 2. – Chest computed tomography showing diffuse alveolar infiltrates, with fine nodules, predominantly in the right upper and the left lower lobes.

never smoked nor been exposed to any known hazardous chemicals or fumes.

On admission, physical examination of the patient revealed mild alopecia and macular erythema on her cheeks. Haemoglobin was 8.3 $g \cdot dL^{-1}$ and erythrocyte sedimentation rate (ESR) 53 $mm \cdot h^{-1}$. White blood cell (WBC) count was 3,600 $cells \cdot mm^{-3}$, with normal differentials. Blood urea nitrogen (BUN) and creatinine, as well as liver function tests, were all within normal limits. Creatinine clearance was 91.5 $mL \cdot min^{-1}$. Urinalysis revealed mild proteinuria (30 $mg \cdot dL^{-1}$) and microhaematuria (2+ blood) without abnormal casts. Tri-iodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) were also within normal range. Antimicrosomal antibody was positive (1:1600) whilst antithyroglobulin antibody was negative.

Several serological studies, including rheumatoid factor, antinuclear antibody, anti-double-stranded deoxyribonucleic acid (dsDNA) antibody, complement levels, cryoglobulins, antistreptolysin O titre, antimycoplasma antibody, and antiglomerular basement membrane antibody (anti-GBM ab) were negative or within normal limits. However, ANCA was detected with a perinuclear pattern (p-ANCA) by indirect immunofluorescence assay. Enzyme-linked immunosorbent assay (ELISA) showed ANCA with myeloperoxidase (MPO) specificity (MPO-ANCA) at a titre of 138 ELISA units (EU)$\cdot mL^{-1}$ (normal <10 EU$\cdot mL^{-1}$). Lymphocyte stimulation assay for PTU was negative.

Chest radiography revealed a reduction of the infiltrates. Arterial blood gas analysis and pulmonary function tests were normal.

Bronchoscopy performed on hospital day 23 revealed no endobronchial lesions. Bronchoalveolar lavage showed abundant haemosiderin-laden macrophages, with normal differential cell count. Cultures for bacteria and fungi were negative. Transbronchial lung biopsy confirmed the presence of haemosiderin-laden macrophages within the alveolar spaces and lung interstitium. No histological features of vasculitis, alveolitis or fibrosis, or granulomatous changes were demonstrated. However, some sections of the basement membranes of the alveolar capillaries stained with periodic acid methenamine silver were unclear. An immunofluorescence study revealed no deposition of immunoglobulins or complements on the alveolar capillaries.

Symptoms and pulmonary infiltrates had resolved completely during the hospitalization, without any treatment. Anaemia, leucopenia and haematuria, as well as proteinuria, also disappeared within several months. Because of the relapse of hyperthyroidism, the patient eventually underwent radioactive iodine treatment. She has been well for 4 yrs without the recurrence of pulmonary haemorrhage or renal disease. The titre of MPO-ANCA decreased to 46 EU$\cdot mL^{-1}$ in February 1993, but remained detectable at 35 EU$\cdot mL^{-1}$ in July 1994, and 44 EU$\cdot mL^{-1}$ in June 1995.

Discussion

This patient developed alveolar haemorrhage and microhaematuria associated with MPO-ANCA during PTU therapy for hyperthyroidism. After withdrawal of the drug, all symptoms resolved, and her long-term clinical course has been excellent.

Alveolar haemorrhage associated with immunological disorders has been classified into three categories, according to immunohistochemical and serological criteria: 1) anti-GBN ab mediated; 2) immune-complex mediated; and 3) ANCA-associated vasculitis [7]. Based upon clinical course as well as the serological and immunofluorescence studies, Goodpasture's syndrome, systemic lupus erythematosus, mixed cryoglobulinaemia, Henoch-Schönlein purpura and poststreptococcus infectious disease were eliminated. The presence of MPO-ANCA strongly suggested that the alveolar haemorrhage and microhaematuria were due to ANCA-associated vasculitis. The histological findings showed no active inflammation. The unclear delineation of the basement membranes of the alveolar capillaries might indicate capillary injury. However, electron microscopic study would be necessary to confirm this. BOSCH and co-workers [8] reported that the detection of p-ANCA or MPO-ANCA in patients with alveolar haemorrhage and renal disease supports the presence of alveolar and glomerular capillary vasculitis.

ANCA-associated vasculitis, including Wegener's granulomatosis and polyarteritis, is usually life-threatening, and rapid introduction of high-dose corticosteroids and immunosuppressive agents are necessary to improve the prognosis. In contrast, the patient studied had an excellent clinical course, without particular treatment once PTU had been discontinued. The titres of ANCA fell with clinical improvement. She also had several symptoms and abnormal laboratory values that were consistent with the well-known side-effects of PTU. These features suggested that the ANCA-associated vasculitis was induced by PTU. We did not attempt to rechallenge the patient with PTU when hyperthyroidism relapsed, since she might redevelop the severe adverse reactions.

PTU-induced vasculitis often occurs within weeks of treatment, but may develop after months or even years. The vascular disorder is not necessarily dose-dependent, and usually improves after discontinuation of the drug, although it occasionally requires immunosuppressive therapy. ANCA-associated vasculitis has been increasingly reported in patients with PTU-induced vasculitis, especially in those with PTU-induced crescentic glomerulonephritis [4, 5]. Recently, ROMAS *et al.* [9] reported a

case with PTU-induced alveolar haemorrhage associated with ANCA specific for MPO and human neutrophil elastase. The patient had no renal involvement, in contrast to the present patient. Some variants may be present within PTU-induced ANCA-associated vasculitis.

Possible mechanisms for the production of ANCA are the interaction between PTU and neutrophils or neutrophil MPO. MPO and hydrogen peroxide produced by neutrophils could metabolize the drug leading to the reactive intermediates that are immunogenic for T-cells and stimulate the immune systems [10]. These metabolites also have cytotoxic activity, leading to cell death and abnormal degradation of self-material, as well as production of autoantibodies [11, 12]. Alternatively, PTU may bind to MPO, changing the haem structure of the enzyme [13], which may then act as an antigen.

Alveolar haemorrhage or pulmonary-renal syndrome associated with antineutrophil cytoplasmic antibody may be a newly described complication of propylthiouracil therapy. Antineutrophil cytoplasmic antibody may be a useful marker for the early detection of propylthiouracil-induced vasculitis. Following detection of this condition, propylthiouracil should be discontinued before other therapeutic measures are initiated.

Acknowledgements: The authors thank T. Yokose, M. Kobayashi and Y. Kawakami for their important advice.

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