CASE REPORT

Diffuse alveolar haemorrhage secondary to propylthiouracil-induced vasculitis

Catarina Ferreira,¹ Teresa Costa,¹ Ana Vieira Marques²¹Pulmonology Department, Centro Hospitalar e Universitário de Coimbra—Hospital Geral, Coimbra, Portugal²Intensive Care Unit, Centro Hospitalar e Universitário de Coimbra—Hospital Geral, Coimbra, Portugal

Correspondence to

Dr Catarina Ferreira, catfer24@hotmail.com

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SUMMARY

Propylthiouracil is a drug used to treat hyperthyroidism. It can cause several side effects including pulmonary disorders that, although rare, can be severe. The authors describe the case of a woman treated with propylthiouracil who developed diffuse alveolar haemorrhage with severe respiratory failure and anaemia, which improved with discontinuation of the antithyroid drug and on starting systemic corticosteroid therapy.

BACKGROUND

Propylthiouracil (PTU) is often used to treat hyperthyroidism. This drug may cause several side effects including pulmonary disorders that, although rare, can be severe.¹

The development of cytoplasmic antibodies (antineutrophil cytoplasmic antibodies, ANCA) is common in patients treated with PTU.^{2–3} However, ANCA-associated vasculitis is rare with pulmonary involvement being possible in this context.^{4–5}

Suspension of PTU and immunosuppressive therapy in severe cases allows remission of vasculitis.^{6–7}

The authors describe the case of a woman treated with PTU who developed diffuse alveolar haemorrhage with severe respiratory failure and anaemia, which improved with discontinuation of the antithyroid drug and on starting systemic corticosteroid therapy.

CASE PRESENTATION

We present the case of a 72-year-old Caucasian woman, non-smoker, retired from a textile factory. She had been medicated for hyperthyroidism (with PTU 50 mg twice daily since 16 months ago) and also had a history of arterial hypertension, dyslipidaemia, osteoporosis and depressive syndrome.

She presented after 8 days of haemoptoic productive cough, bilateral posterior thoracic pain, fever and fatigue.

Physical examination showed pale skin, afebrile and tachypnoea of 26 cycles per min. Pulmonary auscultation revealed crackles in bilateral middle zones. Abdominal examination did not reveal any significant findings.

Laboratory studies showed anaemia with haemoglobin of 8.7 g/dL (normal 12–15 g/dL), normocytic and normochromic; normal white cell and platelet count; elevated C reactive protein 23 mg/dL (normal 0–0.5 mg/dL), lactate dehydrogenase 475 U/L (normal 313–618 U/L), alanine transaminase 87 U/L (normal <31 U/L), aspartate transaminase 88 U/L (normal <34 U/L), alkaline phosphatase 249 U/L (40–150 U/L), c-glutamyl transferase

128 U/L (<38 U/L), kidney function and coagulation studies were normal. Erythrocyte sedimentation rate was elevated: 110 mm/h (normal <35 mm/h).

Arterial blood gas on 2 L/min oxygen by nasal cannula revealed acute hypoxemic respiratory failure with pH 7.47, PaCO₂ 36.8 mm Hg, PaO₂ 63.8 mm Hg, HCO₃ 26.1 mEq/L and SatO₂ 93.7%.

Chest X-ray showed multiple bilateral alveolar infiltrates with perihilar confluence (figure 1). Pneumococcal and *Legionella* urinary antigen tests were negative. Two aerobic blood cultures were also negative. Abdominal ultrasound was normal.

The patient was diagnosed with bilateral community-acquired pneumonia and started on empirical intravenous antibiotic with amoxicillin/clavulanate (2200 mg every 8 h) and azithromycin (500 mg every 24 h).

On the second day of hospitalisation, clinical deterioration occurred with dyspnoea and an episode of moderate haemoptysis. There was also worsening of hypoxemic respiratory failure (arterial blood gas with FiO₂ 40%: pCO₂ 31 mm Hg and pO₂ 39 mm Hg) and radiological worsening with enlargement and spread of alveolar infiltrates. At this time the patient was transferred to an intensive care unit.

INVESTIGATIONS

The diagnosis of diffuse alveolar haemorrhage was assumed and after further studies to investigate the underlying cause being carried out, the patient started therapy with intravenous methylprednisolone 1 g/day.

Immunological study revealed positive myeloperoxidase (MPO; 211.6 IU/mL) and proteinase 3

Figure 1 Initial chest X-ray.

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(PR3) anticytoplasmic antibodies (7.2 IU/mL; positive >20 and >3 IU/mL, respectively). The remaining study including antiglomerular basement membrane antibody, antinuclear antibodies, rheumatoid factor and antibodies to cyclic citrullinated peptide was negative.

CT scan showed extensive bilateral areas of ground glass opacities associated with thickening of the interlobular septa with relative preservation of subpleural areas (figure 2).

Flexible bronchoscopy with bronchoalveolar lavage (BAL) was performed 8 days after starting immunosuppressive therapy and after improvement of respiratory failure using 1.5 L/min oxygen by nasal cannula. BAL revealed no endobronchial lesions or active bleeding. BAL fluid was slightly haematic; differential cell count contained 5% neutrophils, 7% lymphocytes and 88% macrophages with haemosiderin-laden macrophages consistent with alveolar haemorrhage. BAL cultures were negative for bacteria, mycobacteria and fungi. Cytology was also negative for malignant cells.

As the patient was medicated with PTU for several months and this drug is associated with ANCA vasculitis, a causal relationship was established with PTU.

DIFFERENTIAL DIAGNOSIS

The patient presented with bilateral alveolar infiltrates and acute hypoxemic respiratory failure at admission suggesting, as differential diagnosis, community acquired pneumonia, tuberculosis, acute interstitial pneumonia, acute eosinophilic pneumonia, diffuse alveolar haemorrhage, drug-induced pneumonia and pulmonary oedema.

Anaemia could be caused by alveolar haemorrhage, gastrointestinal bleeding, acute inflammation or iron deficiency, among others.

The patient was started empirically on antibiotherapy for possible community-acquired pneumonia.

Diffuse alveolar haemorrhage was assumed because the patient presented haemoptysis and worsening hypoxaemia.

Diffuse alveolar haemorrhage can be caused by a variety of disorders including pulmonary infection, autoimmune disorders (granulomatosis with polyangiitis (Wegener's), microscopic

polyangiitis and anti-glomerular basement membrane disease), collagen vascular disease, drug reactions, cardiac disorders, coagulopathy and idiopathic pulmonary haemosiderosis.

We considered drug-induced alveolar haemorrhage because BAL showed haemosiderin-laden macrophages, and PTU can induce ANCA vasculitis with pulmonary manifestations such as alveolar haemorrhage, and as the other differential diagnoses were excluded by investigation.

TREATMENT

PTU was replaced by metibazol 5 mg twice daily. Methylprednisolone in pulses of 1 g/day was administered for 3 days and then maintenance dose of prednisolone (1 mg/kg/day).

OUTCOME AND FOLLOW-UP

There was good response to therapy with progressive improvement of dyspnoea and no further episodes of haemoptysis. Invasive mechanical ventilation was not needed. The patient remained breathing spontaneously with oxygen (initially with FiO₂ of 50%, which was progressively reduced until ambient air). Analytical and radiological improvement was also seen (figure 3).

Now, nearly 5 months after beginning treatment, the patient is asymptomatic but still under treatment (tapering doses of prednisolone). There was normalisation of the values of haemoglobin, and also of MPO and PR3-ANCA. Chest X-ray showed resolution of alveolar opacities.

DISCUSSION

The authors present a case of PTU-induced autoimmunity with diffuse alveolar haemorrhage as initial manifestation presenting as anaemia, diffuse pulmonary infiltrates and haemoptysis.

Diffuse alveolar haemorrhage is a clinical condition that can be serious and even fatal if not diagnosed and treated early. In most cases it is caused by vasculitis of small pulmonary vessels. There are three major groups:

A. Pauci-immune vasculitis, characterised by lack or shortage of immune deposits in immunofluorescence microscopy and frequent association with pulmonary capillaritis and

Figure 2 CT scan showing extensive bilateral areas of ground glass infiltrates.

Figure 3 Chest X-ray at discharge.

antineutrophil cytoplasmic antibodies. This includes granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss);⁸

- B. Produced by immune deposits, which can be detected by immunofluorescence;
- C. A heterogeneous group that includes various aetiologies such as drug toxicity, infections and idiopathic causes.^{7 9–11} Many drugs can cause diffuse alveolar haemorrhage, including PTU, amiodarone, anticoagulants, nitrofurantoin, penicillamine, hydrazine, all-*trans*-retinoic acid, trimellitic anhydride, isocyanates, cocaine, etoposide, gemcitabine, etanercept, sirolimus and infliximab.¹

The diagnosis of alveolar haemorrhage is based on signs and symptoms, and radiological and serological data. However, diagnosis may be difficult since about one-third of patients do not present the classic triad of bilateral alveolar infiltrates, haemoptysis and anaemia, and do not have associated kidney disease or prior diagnosis of vasculitis or connective tissue disease. So it is important to carry out a careful evaluation of the pharmacological history.^{7 9}

In the present case, diagnostic confirmation of alveolar haemorrhage was made by flexible bronchoscopy and BAL with presence of haemosiderin-laden macrophages. This is the most useful technique for the diagnosis.^{7 11} Owing to severe respiratory failure at presentation, we performed bronchoscopy and BAL on our patient a few days after she had starting immunosuppressive therapy, and after respiratory failure had improved, thus reducing the risk of complications of this procedure and considering that haemosiderin-laden macrophages persist for few weeks.

In the case described, given that our patient was treated with PTU for several months and given that this drug is associated with ANCA vasculitis, a causal relationship with PTU was established.

PTU is an antithyroid drug of the thioamide group. Adverse side effects include elevated liver enzymes, leukopenia, rash and arthralgia. Rarely, it can be associated with vasculitis, accounting for about 93% of thionamide-induced cases.^{3 12}

ANCAs are important serological markers for small vessel vasculitis. Several forms of ANCA are described according to their immunofluorescent patterns. From a diagnostic point of view there are two main standards: classic pattern (c-ANCA) and

perinuclear pattern (p-ANCA). The classic pattern is associated with antiproteinase 3 antibodies (PR3) that produce a cytoplasmic pattern (c-ANCA). It has high specificity (95%) for granulomatosis with polyangiitis (Wegener's) but can also be found in other systemic vasculitides such as eosinophilic granulomatosis with polyangiitis (Churg-Strauss) and microscopic polyangiitis. Antimyeloperoxidase antibodies (MPO) are associated with a fluorescent perinuclear pattern (p-ANCA). This pattern occurs in small vessel vasculitis and necrotising glomerulonephritis.^{7 11 13–16}

PTU can induce positive ANCA vasculitis with polyclonal autoantibodies. Although the origin of these antibodies is not fully understood, it is believed that PTU can accumulate in neutrophils, binding to MPO and changing its structure. This change in configuration of the enzyme can trigger formation of autoantibodies. ANCA-activated neutrophils contribute to the proteolytic and oxidative damage of blood vessels via activation of cells in vitro as monocytes and endothelial cells.^{2 4 10 13 14 7–19} In about 94% of cases this type of immune-mediated vasculitis is associated with the presence of p-ANCA. Positive cases of ANCA-PR3, human leucocyte elastase and lactoferrin have also been described. In the present case we find a situation of overlap with positivity for MPO and PR3, rarely described in the literature.^{3 13 14 20}

Prevalence of ANCA-positive patients treated with PTU ranges from 4% to 46%.^{2 3} Although ANCA are present with relative frequency in these patients, the prevalence of vasculitis is much lower (0–1.4%).^{4 5} Thus the positivity for ANCA does not necessarily predict the onset of symptoms and signs of vasculitis. Similarly, the presence of ANCAs without associated vasculitis indicates that ANCAs alone are not sufficient to induce vasculitis.^{2 13 21}

PTU-induced vasculitis usually occurs a few months after starting this drug, and most often more than 18 months after.^{4 10 22} The rising titre level of ANCAs correlates with further risk of disease but does not predict when it will occur.²³

About three-quarters of cases have been reported in women, which reflects the higher prevalence of thyroid disease in females. The average age of these patients is 44 years.^{4 24}

The most frequent clinical manifestation of vasculitis associated with PTU is renal dysfunction (in 67%) presenting with proteinuria and/or haematuria. Arthralgia was described in 48% of patients, fever in 37% and skin lesions in 30%. Pulmonary manifestations are less frequent occurring in about 26% of patients and include diffuse alveolar haemorrhage, diffuse interstitial pneumonia, bronchiolitis obliterans with organising pneumonia and adult respiratory distress syndrome.^{1 7 13 17 19 20 24–29}

Treatment recommendations for PTU-induced vasculitis depend on the severity of the disease. The first measure is the suspension of the drug. In situations of severe vasculitis with pulmonary manifestations with diffuse alveolar haemorrhage and respiratory failure, as in the case presented, immunosuppressive treatment with systemic corticosteroids at high doses is recommended. There are controversies over whether immunosuppressive agents such as cyclophosphamide should be added to corticosteroids. The addition of plasmapheresis to immunosuppression should be considered if there is severe renal dysfunction and severe diffuse alveolar haemorrhage. Induction therapy should be tapered over several months, although there are no specific guidelines about time and dosage. The precise duration of maintenance therapy thereafter is unclear. In the absence of specific guidelines the therapy can be extrapolated from other causes of alveolar haemorrhage and guided by clinical issues with close monitoring of the patient. In addition

to drug therapy, supportive therapy for respiratory failure will also be needed, often requiring invasive mechanical ventilation.^{6 7 11 19 30}

In general, titres of ANCA correlate with response to treatment and disease activity. Resolution of signs and symptoms and decline in ANCA usually occur with medication withdrawal. However, clinical remission may precede ANCA negatization, with rare cases presenting high or rising ANCA-MPO titres in the remission phase irrespective of clinical recurrence.^{3 5 15 24 30 31}

As positivity for ANCA is high during treatment with PTU and a percentage of patients progress to clinical vasculitis, it is suggested that patients be screened to anticytoplasmic antibodies before starting this drug and periodically during therapy for early disease detection and consequent prognosis improvement.^{4 10 13 26 27}

Learning points

- ▶ Diffuse alveolar haemorrhage is a serious condition that can be fatal if not diagnosed and treated in time.
- ▶ This case aims to highlight the diagnostic challenge of diffuse alveolar haemorrhage and the importance of considering drugs as aetiopathogenic agents of this entity.
- ▶ Immediate recognition of clinical manifestations and suspension of the drug are essential for a good clinical outcome.

Competing interests None.

Patient consent Obtained.

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