Pulmonary haemorrhage and vasculitis in Graves' disease

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Case history

A 30 yr old female nurse of African–Caribbean descent presented at the emergency dept with a 24-h history of haemoptysis and shortness of breath. A dry cough had been present for 2 weeks, with bilateral "pleuritic" chest pain. She described a 3-month history of widespread arthralgia involving both large (knees and hips) and small (hands and feet) joints. For the previous 3 yrs, she had been receiving treatment for hyperthyroidism due to Graves' disease, using propylthiouracil (PTU), a commonly used anti-thyroid drug. A total thyroidectomy had been scheduled. There was no known or contact history of tuberculosis, she had never smoked and she had not travelled outside the UK during the preceding 12 months.

At the time of her admission with haemoptysis, she was taking PTU 150 mg twice daily, as well as naproxen and omeprazole. At admission, she was unwell with tachycardia (110 bpm) and her blood pressure was 142/92 mmHg. She had tachypnoea (respiratory rate of 30 breaths per min) and was hypoxic (arterial oxygen saturation 90% in room air). Widespread crepitations were audible on chest examination, and a diffuse nontender fleshy goitre without a bruit was present. The admission chest radiograph is shown in figure 1.

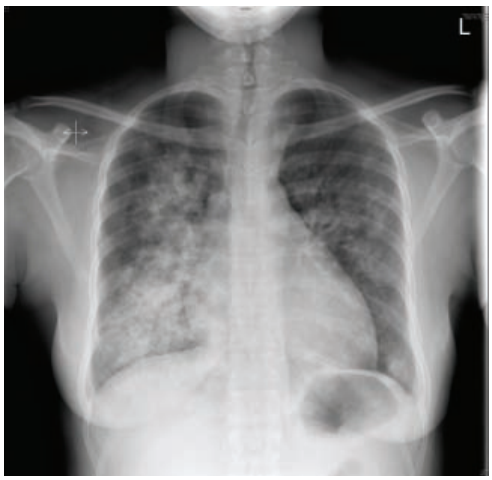


Figure 1
Chest radiography at admission.

Task 1
Interpret the chest radiograph.

HERMES syllabus link: modules B.5.4

Answer 1
Diffuse bronchoalveolar shadowing is visible, most markedly in the right lung field.

Biochemical tests showed anaemia (haemoglobin 10.3 g per dL (normal range 12–15 g per dL) and raised inflammatory markers (C-reactive protein 135 (normal range 0–5)). Urinalysis showed the presence of blood and protein but no dysmorphic red blood cells or casts were seen. The urine protein creatinine ratio was raised at 223 mg per mmol (normal range 0–15 mg per mmol). Renal function was normal. Thyroid-stimulating hormone was suppressed with low free T4 but raised free T3 of 9.0 pmol per L (normal range 3.1–6.8 pmol per L). Anti-neutrophil cytoplasmic antibody (ANCA) against myeloperoxidase (MPO) was strongly positive (titre of 495 U per mL (normal range 0.0–10.0 U per mL). All other autoimmune markers, including anti-glomerular basement membrane antibodies, anti-nuclear antibodies, rheumatoid factor and complement levels were normal. Serial blood and sputum cultures taken at admission did not reveal any infective precipitant or cause for the symptoms. HIV and Mantoux tests were negative.

Task 2
Which of the following are appropriate interventions for this patient?
a) Broad-spectrum antibiotics.
b) Urgent lung function tests.
c) Oxygen.
d) Tranexamic acid.

Answer 2

a) This is a correct answer as severe pneumonia is an obvious possibility.
b) This is not a correct answer as the patient is too unwell for these tests and will not help in the immediate management.
c) This is a correct answer as the patient was quite hypoxic.
d) This is a correct answer as pulmonary haemorrhage is quite likely in the given clinical scenario.

The patient was initially treated with humidified high-flow oxygen (inhaled oxygen fraction 60%), broad-spectrum antibiotics and tranexamic acid. As PTU-induced vasculitis was considered, the PTU was discontinued and substituted with carbimazole.

24 h following presentation, the patient's condition deteriorated with a rising respiratory rate, worsening tachycardia and worsening chest radiography (figure 2). A decrease in haemoglobin (to 7.8 g per dL) resulted in administration of 2 units of whole blood. Bedside transthoracic echocardiography showed good biventricular function with no evidence of a pericardial effusion.

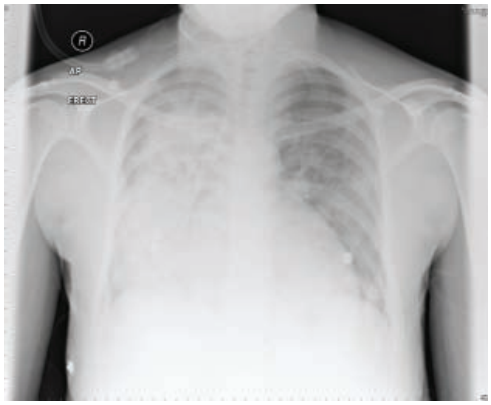


Figure 2
Chest radiography on day 3 after admission.

Task 3
How would you manage this deterioration?

Answer 3

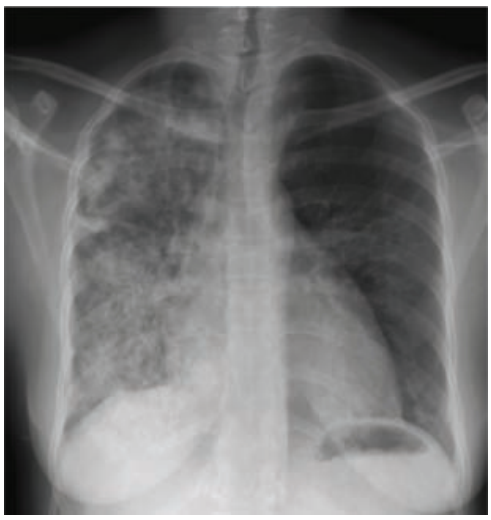
In addition to supportive measures systemic immunosuppressive agents should be started.

Patient was commenced on intravenous pulsed methylprednisolone (1000 mg on day 1 and 500 mg on days 2–4) followed by oral prednisolone (60 mg). She was also commenced on *i.v.* cyclophosphamide (500 mg on day 5). These immune-directed treatments resulted in rapid improvement in clinical wellbeing and resolution of the pulmonary infiltrates on chest radiography (figure 3) and inflammatory markers. The patient was discharged home 2 weeks after admission.

Following discharge from hospital, she received a further five pulses of 500 mg *i.v.* cyclophosphamide at 2-weekly intervals as an outpatient. She was then commenced on weekly methotrexate and her glucocorticoid treatment gradually reduced. The MPO–ANCA titre improved markedly with immunosuppressive therapy (table 1) and this change corresponded with clinical improvement. Near-total thyroidectomy was performed 4 months post-admission and thyroxine substitution commenced.

Table 1 Serial anti-MPO titres

Date	Admission	6 weeks	3 months	4 months	7 months	9 months
Titre U per mL	495	128	61	29.7	21.2	15
Normal range 0–10 U per mL						



9 months after admission, methotrexate was changed to azathioprine as the patient wished to consider further pregnancy. 1 yr after admission, chest radiography had normalised (figure 4) and lung function had significantly improved. Renal function remained mildly impaired, with a creatinine level of 89 µmol per L (estimated glomerular filtration rate of 77 mL per min).

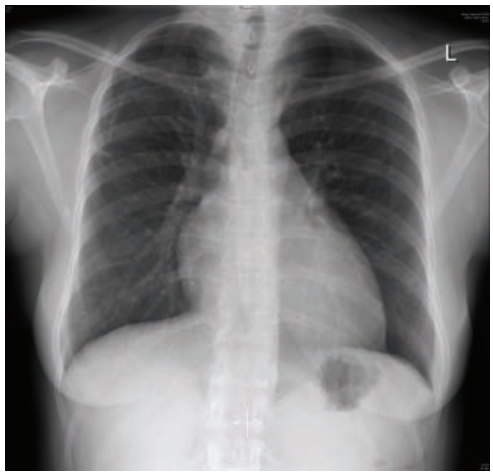


Figure 4
Chest radiography 12 months later.

15 months after presentation, the patient's medication comprises prednisolone 7.5 mg, azathioprine 100 mg and thyroxine 125 µg. Anti-MPO antibody is still present although at a reducing concentration. The patient had returned to work and does not complain of any residual joint pains, myalgia or breathlessness.

Discussion

This case illustrates a rare but serious adverse effect of a drug used commonly in the treatment of Graves' disease. Despite first being reported in 1992 [1], awareness of the condition remains limited, which warrants continued education of the medical community.

ANCA-associated vasculitides are a rare complication of thionamide (PTU and methimazole) therapy. The condition was first reported in 1992 by Stankus and Johnson [1], and to date over 40 such cases have been reported [2]. However, awareness of the condition remains limited with the potential for delayed diagnosis and adverse clinical consequences as described above. This is particularly important as early diagnosis and cessation of thionamide anti-thyroid medication are likely to lead to a complete remission without the need for prolonged immunosuppressive therapy.

Reported rates for the incidence and

prevalence of positive ANCA associated with anti-thyroid medications vary. In a recently published study, 28 newly diagnosed patients with Graves' disease treated with PTU were followed up at 3-monthly intervals for 2 yrs [3]. Pre-treatment ANCA was negative in all subjects. Nine (32.1%) out of the 28 developed measurable ANCA following a mean PTU treatment duration of 11.7 months. None of the patients had systemic vasculitis-like symptoms. In contrast, NOH *et al.* [4], who previously studied 73 untreated patients with Graves, found only three (4.1%) patients positive for MPO–ANCA after >13 months of PTU treatment. Only one of these three patients developed a vasculitic illness, which resolved after cessation of PTU therapy. In a study by GUNTON *et al.* [5] involving 30 patients receiving anti-thyroid medications over 18 months, a positive ANCA was found in eight (26.7%) patients. Seven out of eight patients were on PTU at the time and one was on carbimazole. The average duration of PTU therapy was 7.9 yrs. Out of these eight patients, three developed symptoms of arthralgia and myalgia, which resolved after cessation of PTU. Interestingly, it appears that those patients who do develop clinical vasculitis tend to have a higher titre and avidity of anti-MPO antibodies than those with no overt clinical symptoms. These patients have also been on PTU therapy for longer [6]. Following cessation of PTU, both the avidity and the titre of MPO-ANCA antibodies tend to decrease significantly. It has been suggested that the avidity falls much more quickly than the titre [7].

Renal dysfunction and joint involvement are the most common presenting symptoms of anti-thyroid medication-induced ANCA-positive vasculitides. However, patients can have varying presentations depending on the organ involvement, with other presenting features including fever, malaise, erythema, rash, scleritis, epistaxis, skin ulcers and pericarditis [2].

Haemoptysis as a consequence of pulmonary haemorrhage secondary to PTU induced vasculitis as a presenting complaint is unusual but has been reported previously in several previous case reports [8, 9]. Other respiratory manifestations may include acute respiratory distress, pulmonary infiltrates and hilar adenopathy.

Most patients who develop anti-thyroid drug-induced vasculitides are female, but this may be because thyrotoxicosis is more common in females. In >90% patients with this complication, there is a specific ANCA staining pattern which is peri-nuclear (p-ANCA) with MPO as the major antigen. PTU is the responsible agent in over 90% of these cases [7].

The pathogenesis of PTU-induced vasculitis is not clear but MPO–ANCA might be one of the contributing factors. Other suggestions include alterations of the configuration of MPO by PTU that promotes autoantibody formation, dose-dependent inhibition of MPO oxidation activity and conversion of PTU into cytotoxic substrates by activated neutrophil hydrogen peroxidase and MPO [10]. In addition to PTU, several other drugs are also known to cause drug-induced vasculitis [11]. There are at least two case reports of proton pump inhibitor therapy associated with ANCA-associated vasculitis [12, 13]. Our patient was on omeprazole, but we felt clinically that this was unlikely to be the offending drug. She was continued on this drug for prevention of stress ulceration associated with acute severe illness and high-dose steroid treatment. Furthermore, her clinical course and ANCA titres improved despite continuation of this drug.

There are no established guidelines on the management of PTU-induced ANCA-associated vasculitis. Treatment should be guided by clinical severity. PTU should be discontinued at the earliest clinical suspicion of the condition. Alternative anti-thyroid medication including carbimazole or methamizole can be used if needed. Alternative nondrug treatment options such as radioiodine therapy or thyroid surgery should also be considered in appropriate cases. Fever, myalgia, arthralgia and other constitutional symptoms are likely to respond to simple cessation of PTU. Patients with severe disease manifestations such as renal involvement and pulmonary haemorrhage require systemic immunosuppressive therapy with steroids and cyclophosphamide. However, there is no consensus about either the optimal immunosuppressant or the duration of treatment.

This case illustrates a rare but serious adverse effect of a widely used treatment for Graves' disease and emphasises the need for endocrine and general physicians to be aware of this potentially serious complication of treatment. We have described serial changes in MPO–ANCA titres following treatment which appear to track clinical improvement and response to therapy: MPO–ANCA titre may thus be a useful marker of PTU-induced vasculitis and an index for monitoring treatment response. We have also described the long-term clinical course of this severe adverse effect of PTU. This case highlights the need for a multi-disciplinary approach for the management of such cases.

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