CASE REPORT

A 27-year-old woman presenting with refractory hypoxaemic respiratory failure, haemoptysis and thyrotoxicosis: a rare manifestation of propylthiouracil therapy

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SUMMARY

Pulmonary manifestations of hyperthyroidism not only include pulmonary hypertension and hydrostatic pulmonary oedema, but also treatment/drug-associated pulmonary diseases have to be considered as an exclusion diagnosis. A 27-year-old woman with hypoxaemic respiratory failure under an arterial-venous extra-corporeal membrane oxygenator (AV-ECMO) was admitted to the intensive care unit (ICU). The patient had progressive dyspnoea with haemoptysis, palpitations and failure to thrive. The patient had Graves' disease treated previously with propylthiouracil (PTU). Diffuse alveolar haemorrhage is a non-specific syndrome characterised by evidence of diffuse alveolar damage, exclusion of infectious aetiology and progressively bloodier bronchoalveolar lavage (and/or 20% hemosiderin laden macrophages on cytological examination). PTU associated perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) vasculitis appears to be more common in younger female patients presenting with leukocytoclastic vasculitis, myalgias and arthralgias. The latter compared to non-drug associated ANCA vasculitis which are more common in older males with visceral involvement. PTU-induced ANCA vasculitis prognosis appears to be better compared to primary ANCA syndromes.

BACKGROUND

Propylthiouracil (PTU)-associated perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) vasculitis is rare but appears to afflict younger female patients presenting with leukocytoclastic vasculitis, myalgias and arthralgias. Acute respiratory distress syndrome with refractory hypoxaemia is an even more uncommon presentation of the drug's immunogenic potential.

CASE PRESENTATION

A 27-year-old Mexican woman presented with hypoxaemic failure to the intensive care unit (ICU). Three weeks earlier, the patient had progressive dyspnoea with haemoptysis, palpitations and failure to thrive. The patient had Graves' disease that was previously treated with PTU.

Before arrival at the ICU from another hospital, the patient had a right pneumothorax due to barotrauma. In addition to right tube thoracotomy, the patient had placement of arterial-venous extra-corporeal oxygenator membrane (AV-ECMO)

cannulas bilaterally at her femoral vessels. Patient was complicated further with left lower extremity acute ischaemia and underwent endovascular common femoral artery thrombectomy.

Blood pressure was 104/40 mm Hg on multiple vasoactive medications. Heart rate was 134 bpm with sinus tachycardia. The patient was sedated with anasarca, as she had bilateral inspiration crackles, without a murmur or rub. Extremities were cold with diminished pulses. Goal-directed ultrasound examination revealed a hyperdynamic left ventricle and a moderately dilated right ventricle. Lungs had bilateral B-lines superior-anteriorly. Bilateral lung consolidations were found inferior-posteriorly.

INVESTIGATIONS

Study findings included the following: pH: 6.97, pCO₂: 62.7 mm Hg, PaO₂: 310 mm Hg while on positive end expiratory pressure 12 cm H₂O plus AV-ECMO. WCC: 30.99 k/μL with 91% neutrophils, haemoglobin 10.1 g/dL, platelets 290 k/μL. International Normalised Ratio was 2.6 and a partial thromboplastin time of 41.1 s. Troponin was 2.35 ng/mL. Thyroid-stimulating hormone <0.01 μIU/mL. Electrolytes revealed potassium of 4.9 mEq/L, bicarbonate of 20 mEq/L and creatinine of 1.3 mg/dL. Brain natriuretic peptide was 784 ng/mL.

Lingular bronchoalveolar lavage revealed a bloody return with 73% neutrophils. Transbronchial biopsies were not obtained. Cultures were negative for acid-fast bacilli, fungal, nocardia, legionella, viruses. Serology returned negative for HIV, hepatitis panel, antinuclear antibody, Scl-70, SS-A/SS-B and rheumatoid factor. C3 and C4 levels were reduced. p-ANCA was elevated (1:80) along with the myeloperoxidase (MPO) ELISA assay (26 IU).

DIFFERENTIAL DIAGNOSIS

The patient presented with multiple organ dysfunction, hypoxaemic respiratory failure associated with haemoptysis and refractory hypoxaemia requiring AV-ECMO support in the setting of thyrotoxicosis. In an effort to find a unifying diagnosis, pulmonary manifestations in hyperthyroidism include: pulmonary hypertension, respiratory muscle weakness and cardiogenic/hydrostatic pulmonary oedema due to the high-cardiac output state. Also considered in the differential diagnosis are non-cardiogenic

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pulmonary oedema aetiologies, acute eosinophilic pneumonia and diffuse alveolar haemorrhage.

TREATMENT

The patient was empirically covered with broad spectrum anti-bacterial antibiotics until cultures were finalised negative. She was started on high-dose methylprednisolone and then weaned to prednisone 60 mg orally daily.

Plasmapheresis was administered for 5 days. The patient was administered methimazole to decrease production of T₄ and T₃. Unfortunately, she developed left lower extremity gangrene and underwent above the knee amputation. The patient underwent tracheotomy for gradual mechanical ventilation weaning and remains on intermittent haemodialysis due to anuric acute kidney failure.

OUTCOME AND FOLLOW-UP

Six weeks later, the patient was discharged home having recovered renal function and there being no need for intermittent renal replacement therapy.

DISCUSSION

Diffuse alveolar haemorrhage is a syndrome without specific and radiological features defined by widespread alveolar injury suggested by the presence of multilobar pulmonary infiltrates, abnormal gas exchange represented by an increased alveolar-arterial gradient or decreased PaO₂/FiO₂ ratio in the absence of infectious evidence.¹ Lastly, a progressively bloodier return from three separate subsegmental bronchi and/or a cytological examination finding more than 20% haemosiderin laden macrophages is indicative of the syndrome.¹

The immunofluorescence assay used in this case showed p-ANCA reactive with MPO. There is a 10% chance of obtaining a false positive due to similar immunofluorescent staining from other antigens.² The latter was confirmed by a positive ELISA-mediated assay for MPO antibodies. ANCAs are associated with granulomatosis with polyangiitis (formerly Wegener's disease), the Churg-Strauss syndrome, microscopic polyangiitis, 'renal limited vasculitis' and certain drug-induced vasculitic syndromes.² There are several drugs which have been associated with drug-induced ANCA vasculitis: PTU, methimazole, hydralazine, minocycline, phenytoin, etc. PTU-associated vasculitis stands as the most common among drug-induced aetiologies.³

PTU associated p-ANCA positivity has been described in case series to be prevalent in 15–64% of patients.³ PTU-induced ANCA vasculitis is less common (0.47–0.71 patients per 10 000 patients with Graves' disease). Its pathogenesis has been hypothesised through several mechanisms³: (1) chemical structural similarities between PTU and human myeloperoxidase. (2) the MPO-PTU complex acting as a hapten. (3) Antigenic PTU metabolites. Clinically, it has been reported that PTU-induced-vasculitis generally occurs in younger female patients (compared to primary p-ANCA syndromes in which older male patients are commonly affected). The severity of illness is milder in the PTU-induced disease compared to the primary form. Usually, PTU-induced disease presents with

malaise, fatigue, myalgias, arthralgias and skin findings consistent with leukocytoclastic vasculitis.³ In addition, PTU has been reported to have caused bronchiolitis obliterans organising pneumonia in a female patient. This patient improved without relapse after the culprit drug was stopped.⁴

Diagnosis is usually confirmed by cutaneous, kidney or trans-bronchial biopsies along with PTU exposure and a compatible clinical setting. It represents a diagnosis of exclusion after infectious, malignancy or other connective tissue disorders have been ruled out as aetiologies.⁵ Recommended treatment includes: withdrawal of the culprit drug, steroids (amount depending on the severity of illness), cyclophosphamide and plasmapheresis (for severe presentations: rapidly progressive glomerulonephritis and/or interstitial lung disease causing respiratory failure). Expert opinion and small case series expect a better clinical response, prognosis and relapse probability compared to the primary ANCA syndromes.⁵

Learning points

- ▶ Pulmonary manifestations of hyperthyroidism include not only pulmonary hypertension and hydrostatic pulmonary oedema, but also treatment/drug-associated pulmonary diseases have to be considered as an exclusion diagnosis.
- ▶ Diffuse alveolar haemorrhage is a non-specific syndrome characterised by evidence of diffuse alveolar damage, exclusion of infectious aetiology and progressively bloodier bronchoalveolar lavage and/or 20% haemosiderin-laden macrophages on cytological examination.
- ▶ Propylthiouracil (PTU)-associated perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) vasculitis appears to be more common in younger female patients presenting with leukocytoclastic vasculitis, myalgias and arthralgias.
- ▶ The latter compared to non-drug-associated ANCA vasculitis which are more common in older males with visceral involvement. PTU-induced ANCA vasculitis prognosis appears to be better compared to primary ANCA syndromes.

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