Recurrent adult respiratory distress-like syndrome associated with propylthiouracil therapy

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Propylthiouracil (PTU) is widely used for the treatment of thyrotoxicosis. Many side-effects have been reported, in particular transient granulocytopenia and agranulocytosis [1], hepatitis, vasculitis and systemic lupus erythematosus (SLE)-like syndrome [1, 2]. Lung involvement related to PTU has been reported in a small number of patients: interstitial pneumonitis presenting with cough, productive sputum, exertional dyspnoea and hypoxaemia in two patients [3], cavitating lung lesions with generalized vasculitis in three [4, 5], and pleural effusions with SLE-like disease [6, 7]. We report the occurrence of recurrent episodes of an adult respiratory disease-like syndrome (ARDS) associated with an SLE type reaction in a patient treated with PTU.

Case report

A 56 yr old woman was admitted to the hospital because of severe dyspnœa. Hyperthyroidism had been diagnosed 17 yrs previously. Neomercazole was given for 8 yrs and subsequently replaced by PTU (150 mg·day⁻¹). Dry cough, conjunctivitis and rhinitis started 8 yrs before admission, thus approximately one year after PTU treatment began. These were considered to be due to allergic reactions to various pollens and dusts. Nine months before hospitalization, the patient began to feel ill and short of breath, and had fever (38°C). A week later, her temperature was 40°C and a chest radiograph showed diffuse bilateral infiltrates. The patient did not improve after a 3 day course of amoxycillin. After 24 h of steroid therapy (prednisone 50 mg·day⁻¹), she felt better and the fever disappeared. The lung infiltrates cleared in six days. A rash followed this episode; skin testing indicated penicillin allergy. Over the next three months, the patient suffered from malaise and migrating arthralgias without arthritis, and had purpuric skin lesions over the knees, whilst still being treated with PTU (150 mg·day⁻¹).

Six months before admission, the patient was hospitalized after a road traffic accident with multiple fractures (right wrist, and combined tibial and peroneal fractures). She rapidly developed an acute respiratory failure requiring mechanical ventilation for three weeks. The clinical picture was that of an ARDS-like syndrome: arterial oxygen tension (Pao₂) 7.2 kPa, inspired oxygen fraction (FlO₂) 70%. There was no evidence for thrombocytopenia, retinal lesions, conjunctival and upper body petechia, confusion or fat in sputum or urine at any time. The patient recovered slowly over a period of four months without steroid treatment. However, PTU therapy had been stopped on admission. PTU (150 mg·day⁻¹) was reintroduced when the patient left the hospital. Six weeks later, she was readmitted for her third episode of respiratory failure, presenting with fever and progressive dyspnœa.

On admission, the patient appeared acutely ill. She was tachypnoeic (35 breaths·min⁻¹) and her temperature was 40°C. The thyroid gland was slightly enlarged and there was bilateral exophthalmos. Blood pressure was 150/80 mmHg, pulse 142-min⁻¹. Crackles were heard over both lungs. She was severely hypoxemic (Pao₂ 3.2 kPa; FlO₂ 50%) and required immediate assisted ventilation. The erythrocyte sedimentation rate was 130 mm·h⁻¹, Hb 100 g·l⁻¹, total whole blood count (WBC) 11×10⁹·l⁻¹, with normal differential count and platelets 315×10⁹·l⁻¹. Electrolytes, renal and liver function tests were normal. No immune complexes were detected by a fluid phase Ciq-binding assay, complement was in the normal range, and immunoglobulin G (IgG) level was 16.6 g·l⁻¹ (normal range: 5.8–13.3 g·l⁻¹). The following
auto-antibodies were negative: IgM rheumatoid factors, antinuclear antibodies, anti-deoxyribonucleic acid (DNA) antibodies by the crithidia lucilliae assay, antigastric, antithyroglobulin, antimicrosomal, antimitochondrial, antismooth and striated muscles, antiRo, antiSm, antiRNP, antiglomerular-basement membrane antibodies. Serum T4 was 57 nmol·l⁻¹ (normal range: 58–140 nmol·l⁻¹), and T3-resin uptake was 0.22 (0.27–0.36). The ¹³¹Iodine thyroid uptake was slightly increased (45% at 24 h).

The patient was well, the sedimentation rate had decreased to 32 mm·h⁻¹, and the IgG level was normalized to 11.7 g·l⁻¹. A lymphocyte stimulation assay for PTU remained negative. The patient’s follow-up for a period of 5 yrs was devoid of any of her previous complaints. Pulmonary function tests are at present normal.

Discussion

This patient, treated with PTU for many years because of Grave’s disease, suffered on three separate occasions from an ARDS-like episode. No triggering factor was identified for two of these episodes. Once, it followed trauma with multiple fractures. It is difficult to formally exclude trauma as the cause of that particular episode, but we were unable to prove a clear relationship between the trauma and the ARDS: ARDS occurred immediately after trauma, there was no evidence for fat embolism and, as for the two other ARDS-like episodes, the initial complaint was malaise with fever. The second episode was clearly preceded by arthritis and purpura: these features suggested that the ARDS-like episodes were not isolated, but part of a generalized reaction.

Different reasons suggested the PTU was responsible for these recurrent attacks of ARDS: 1) PTU is known to cause various autoimmune reactions, including urticaria and purpura, arthralgia, and SLE-like disease [1, 2]. ARDS may be part of an autoimmune process as well [8]: the occurrence of ARDS in SLE, albeit rare, has been well established [9]; 2) the ARDS-like episodes in our patients were closely linked to PTU prescription. The first episode occurred after several years of treatment; although allergic reactions to PTU occur, usually within weeks or months of initiation of therapy, they are also known to occur after years of uncomplicated treatment [1]. The third episode, clinically similar to the first, followed the reintroduction of the drug within some weeks. However, the most compelling evidence was that the disease completely vanished after stopping PTU: there was no recurrence of lung disease or systemic symptoms during five years. A drug challenge test was considered unethical [4]. Finally, the response to steroids was spectacular with rapid clinical improvement and disappearance of the lung infiltrates (first and third episodes). Of interest was the second episode which lasted several weeks: the patient did not receive steroids, and the allergic reaction may have abated solely because PTU had been stopped on admission.

A favourable response to corticosteroids is very unusual in ARDS due to infection, trauma, fat embolism etc., but is classically reported in severe lung disease associated with SLE [9, 10].

References


