EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2015.0079

Case Report

Propylthiouracil-induced alveolar hemorrhage

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Abstract

Thionamide induced vasculitis is a multisystem disease. The patients may present with different clinical signs and findings due to organ involvement. These patients are almost always perinuclear antineutrophil cytoplasmic antibody (pANCA) or antimyeloperoxidase (MPO) positive. Clinical findings are not seen in all of the patients who are ANCA positive while using thionamide. Although symptoms usually resolve with drug discontinuation, some patients, however, require high-dose steroids, immunosuppressants, or plasmapheresis. We present here a case of alveolar hemorrhage induced by propilthiouracil (PTU) during treatment with PTU for Graves' disease; patients completely recovered with corticosteroid, cyclophosphamide, and plasmapheresis.

Keywords: Vasculitis, propylthiouracil, ANCA

Introduction

Propylthiouracil (PTU) is widely used for treating hyperthyroidism. Vasculitis induced by PTU is a multisystem disease-associated p-ANCA positivity (1). Clinical findings are not seen in all the patients developing ANCA positivity; they may present with different clinical signs due to organ involvement. The most common clinical findings are renal dysfunction and arthralgia. Other clinical findings include fever, fatigue, erythema, rash, alveolar hemorrhage, scleritis, purpura, nasal bleeding, skin ulcerations, pericarditis, and vasculitis of the central nervous system (CNS) (1). The most common pulmonary finding is alveolar hemorrhage (2). The findings usually recover following medication discontinuation but some patients require high-dose corticosteroids, immunsupressants, or plasmapheresis. The condition rarely results in death (3).

Case Presentation

A 40-year-old female patient presented with hemoptysis, fatigue, dyspnea, and palpitations over the past 10 days. On systemic examination, no fever, shivering, skin rashes, night sweats, post-nasal discharge, hematuria, or melena were found. Her history revealed that for 6 years, she had taken PTU for Graves' disease. She was not taking any other medication. At the time of admission, blood pressure was 90/50 mmHg, heart rate: 106 bpm, respiratory rate: 28 per min, and body temperature: 36.8°C. Her conjunctivas were pale, bilateral inspiratory rales were heard on pulmonary auscultation. The palpability of the thyroid gland grade 2, and the patient had exophthalmoses. Temporal artery was not tender on palpation. Baseline laboratory investigations revealed normocytic anemia. Other laboratory findings were as follows: hemoglobin (Hb): 7.1 g/dL (normal reference range: 13.6-17.2 g/dL), white blood cell count: 11300 per cubic millimeter (5200-12400), neutrophils: 79.4% (41%-73%), lymphocytes: 14.8% (19.4%-44.9%), monocytes: 5.4% (5.1%-10.9%), eosinophils: 1% (0.9%-6%), creatinine: 1.1 mg/dL (0.6%-1.3 mg/dL), C-reactive protein (CRP): 41.7 mg/dL (0-10 mg/dL), erythrocyte sedimentation rate (ESR): 23 mm/h (1-13 mm/h). Urinanalysis showed no hematuria. Microscopic examination of the urine showed dysmorphic erythrocytes and erythrocyte cylinders. Occult blood in the feces was negative, thrice. The patient was administered 2 units of erythrocyte suspension and Hb level raised to 9.6 mg/dL. Both chest radiogram and computerized tomography (CT) revealed findings consistent with widespread alveolar hemorrhage. No bacteria grew on the blood and phlegm cultures; tests for acid-fast bacilli were negative, which were tested for thrice. In further laboratory investigation TSH was 0.04 uIU/mL (0.34-4.2 uIU/mL), fT4 1: 55 ng/dL (0.61-1.12), fT3: 3.08 pg/mL (2.5-3.9), antithyroid peroxidase antibody (anti TPO): 54.5 IU/mL (0-35), antithyroglobulin: 50 IU/mL (0-115), antinuclear antibody (ANA) was negative, antineutrophilic cytoplasmic antibody (ANCA) was positive, and p-ANCA was positive. Antiproteinase 3, rheumatoid factor (RF), antiglomerular basal membrane antibody (anti GBM), antidouble strained DNA antibody, anti-Smith antibody, and anti RNP antibody were all negative. Bronchoscopic findings were consistent with alveolar hemorrhage, with the respiratory tract being normal except for alveolar hemorrhage. Lung biopsy was not performed because of apparent alveolar hemorrhage and lowered oxygen saturation; instead, bronchoalveolar lavage (BAL) was done. BAL report indicated benign cytology and presence of hemosiderin-loaded macrophages. Bronchoalveolar lavage culture was negative. CT of the

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Submitted: 05.08.2014
Accepted: 01.10.2014
Available Online Date: 31.03.2015

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paranasal sinuses was normal. Pericarditis was absent on echocardiography and audiometry was normal. PTU was discontinued. Hemoptysis did not regress over the next 2 days. The patient was administered pulsatile steroid treatment at 1 g/day upon progression observed on the anteroposterior pulmonary radiogram (and because no other necrotizing vasculitides were included) and continued after 3 days. During the follow-up period, steroid treatment was continued at 1 mg/kg/day. Hemoptysis partially regressed; however, 5 sessions of plasmapheresis with an interval of 2 days and a single dose cyclophosphamide at 750 mg/m^2/month were added to the treatment regime because of reduced Hb values (8.4 mg/dL) and persisting dyspnea. With this triple treatment regime, it was observed that clinical findings as well as chest radiogram findings recovered significantly. It was observed that ESR reduced to 10 mm/h (normal range: 1-13 mm/h), CRP decreased to 8 mg/L, and control direct urine microscopy revealed that dysmorphic erythrocytes disappeared. Renal biopsy was not performed because erythrocytes disappeared in direct microscopic examination of urine and renal function tests remained stable during the clinical follow-up period of the patient. Thyroid function tests revealed continuing subclinical hyperthyroidism; thus, permanent surgical treatment was scheduled.

Discussion

Thionamides are widely used for treating hyperthyroidism. Their side effects include skin reactions, arthralgia, gastrointestinal events, abnormal gustation and olfaction, sialadenitis, antithyroidal arthritis syndrome, agranulocytosis, thrombocytopenia, aplastic anemia, hepatitis, cholestasis, hypothrombinemia, hypoglycemia (autoimmune insulin syndrome), and pancreatitis. ANCA-associated vasculitis due to PTU is a rare complication (4).

Mechanism of the PTU-induced ANCA (+) vasculitis hasn't been fully understood. Human antimyeloid peroxidase (MPO) and anti TPO antibodies are products of the same gene family and their nucleotide and amino acid chains are similar (5). In thyroid patients with positive anti TPO antibodies, it may be considered that cross-reactivity has developed against MPO and antibodies to MPO and TPO may be concurrently detected in these patients (6). This leads to MPO being released from neutrophil granules stimulated secondarily to a viral infection to be metabolized to cytotoxic side-products of PTU (7). According to another theory, PTU is converted by MPO to PTU-sulfate which is immunogenic for the T cells. It also activates B cells and mediates vascular injury (8). According to another theory, PTU may act as a hapten by interacting with MPO to change its structure (9).

ANCA(+) vasculitis induced by the thionamides has been well defined in the literature. ANCA(+) vasculitis due to PTU, in 1993 (2). Our patient presented with a clinical course of systemic disease consisting of diffuse alveolar hemorrhage and dysmorphic erythrocytes in the urine. Considering the diseases presenting with lung and kidney involvement, one should remember first Goodpasture's syndrome, Wegener granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis. These diagnoses were considered in our patient because CT scanning of the paranasal sinuses was normal, c-ANCA negative, p-ANCA positive, anti GBM negative, and lack of asthma and eosinophilia in the peripheral blood smear, history of abdominal pain, occult blood in the feces, and cutaneous findings. This clinical condition was considered to be consistent with ANCA(+) vasculitis due to PTU reported in the literature. Our patient had a course of vasculitis that was resistant to discontinuing PTU and steroid treatment, which resolved completely with plasmapheresis.

A study by Pillinger et al. (3) recruited 23 patients with vasculitis due to PTU and reported that symptoms disappeared after discontinuing the medications in majority of the patients although immunosuppresssants and dialysis were required in 6 and 1 patients, respectively, and 1 patient died (2). Furthermore, the most common pulmonary finding was alveolar hemorrhage (4 patients) but adult respiratory distress syndrome, upper respiratory tract vasculitis, pulmonary infiltration, and hilar lymphadenopathy were also observed in the patients. Nine of 23 patients were p-ANCA positive, 1 was c-ANCA positive, and 3 were not tested.

The patients may present with different clinical signs and findings due to organ involvement. In another study by Gunton et al. (10) including 27 patients, the most common findings were renal involvement in the form of nephritis or acute renal failure (66,7%) followed by arthralgia (48%), fever (37%), skin findings (29.6%), respiratory tract findings (25.9%), myalgia (22.2%), and scleritis (14.8%) Clinical findings recovered obviously on discontinuation of the medication but treatment with steroids and cyclophosphamide were recommended for the patients with renal failure, and plasmapheresis for those with life-threatening alveolar hemorrhage (3).

p-ANCA is almost always positive in these patients. But clinical findings may not develop in all patients developing ANCA positivity, during PTU treatment. One study retrospectively investigated 73 patients for p-ANCA positivity development during PTU treatment and found that 3 patients developed p-ANCA positivity and 2 of these patients p-ANCA titres normalized, despite continuing PTU treatment and 1 patient developed oral ulcerations, fever, arthralgia, and diarrhea (11).

In conclusion, independent of its mechanism, the relationship between PTU and ANCA(+) vasculitis has been well defined. PTU is a widely used drug. The drug should be discontinued when clinical findings of the disease develop in ANCA(+) patients. ANCA screening is not recommended in all patients using PTU. Physicians should suspect ANCA(+) vasculitis induced by PTU when a systemic disease such as vasculitis develops in a patient using PTU.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.A.; Design - B.A.; Supervision - O.A.; Materials - H.K.; Data Collection and/or Processing - A.A.; Analysis and/or Interpretation - B.K.K.; Literature Review - N.D.; Writer - B.A.; Critical Review - M.S.

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support

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