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CASE REPORT

PROPYLTHIOURACIL-INDUCED SEROPOSITIVE VASCULITIS WITH ALVEOLAR HEMORRHAGE

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ABSTRACT

Propylthiouracil (PTU) is a commonly used anti-thyroid medication. As a rare complication, PTU can induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), resulting in nephritis and alveolar hemorrhage. Here we presented a 52 years old Ethiopian woman who developed AAV during her PTU therapy for toxic goiter. Her clinical, laboratory, and chest imaging were all consistent with the diagnosis. She showed marked improvement after discontinuation of the medication and the addition of corticosteroid and cyclophosphamide. Our case, the first in Ethiopia, illustrates the importance of attentiveness, early identification, and management of this rare side effect of PTU therapy.

***KEY WORDS**: Propylthiouracil, ANCA, Vasculitis, Alveolar Haemorrhage*

INTRODUCTION

Propylthiouracil (PTU) is a common medication used to treat thyroid disorders. A high percentage of patients on this medication have antineutrophil cytoplasmic antibodies (ANCA). However, only a few of these patients develop ANCA-associated vasculitis (AAV), manifesting with alveolar hemorrhage (DAH) and glomerulonephritis [1-4]. We present the first reported case in Ethiopia of a 52-year-old woman who experienced AAV during PTU therapy for a toxic goiter.

Case Presentation

A 52 years old Ethiopian woman who has been taking PTU for the past three years for toxic goiter**,** linked to our pulmonary clinic for cough and blood-tinged sputum, headaches, and easy fatigability of 2 weeks duration. Given her clinical presentation and abnormal CXR (bilateral lower lobe infiltrates), she was initially treated by her primary care physician with antibiotics (ceftriaxone and azithromycin) for pneumonia.

She failed to clinically improve and was referred to our Chest Clinic for further evaluation. Additional history revealed a PTU dose of 100 mg daily, essential hypertension on nifedipine, and previously treated hepatitis C with a sustained viral response.

On evaluation, her vital signs were as follows: BP 125/85mmHg, RR 22bpm, PR 111bpm, T 36.5^{o}C, and SO2 95% on room air at rest.

Her physical examination was significant for pale conjunctiva, anterior neck mass (nodular goiter), and bibasilar crepitation. Initial laboratories revealed a WBC count 4.7× 10^9/L [3.6-10.2×10^9/l], hemoglobin 8.1g/dl [12.5-16.3g/dl], and platelets count 382 × 10^9/L [152-348×10^3/l]; thyroid function test, electrolytes, liver function test and coagulation profile were all normal.

Additional laboratory testing suggested a moderate microcytic hypochromic anemia (mean corpuscular volume 79.2Fl (80-100Fl); serum iron 20 ug/dL(50-150ug/dl); ferritin 61.31 ng/mL(12-150ng/ml); and total iron-binding capacity 276 ug/d(250-450ug/dl). Other pertinent additional results included an elevated ESR (120mm/hr [1-10mm/hr]), elevated CRP (12mg/l [0-1mg/l], abnormal urine analysis +2 RBC/high power field and +2 protein without cast, and negative RT-PCR for COVID-19. The initial non-contrast Chest computer tomography (CT) scan revealed multifocal ground-glass opacities (GGO) in the periphery of both lungs, predominantly the right middle and both lower lobes (Figure 1). Echocardiogram was normal. She was treated with supplemental iron while awaiting further investigations.

Several days later at Chest Clinic, the patient complained of persistent blood-tinged sputum and worsening dyspnea. She was now hypoxemic on room air (O2 sat 85% at rest) with progressive bilateral crepitations.

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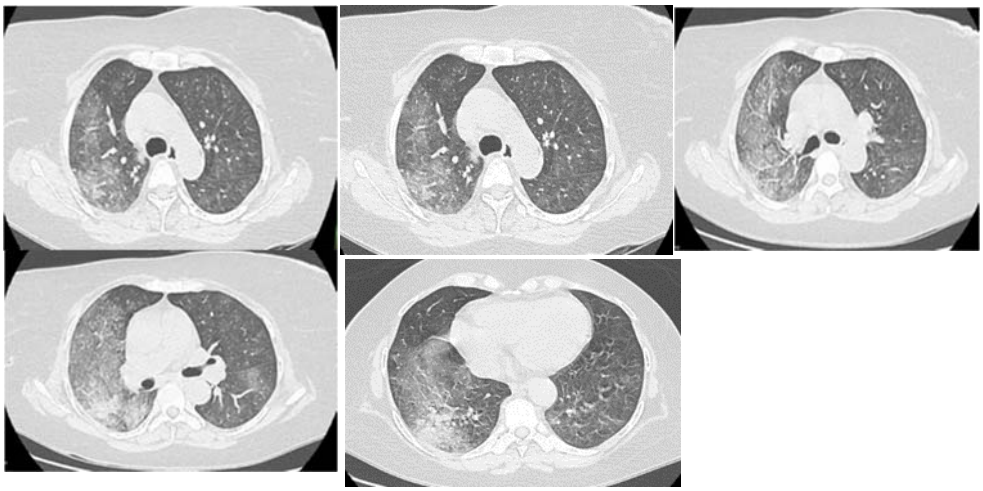

Figure 1. Axial lung windows of the high-resolution chest CT scan (was done on first clinic visit) revealed predominantly right middle and lower lung fields alveolar fillings with ground-glass opacification and some patchy area in left lung GGO.

The patient's anemia had also worsened (hemoglobin 7.5 mg/dl [12.5-16.3g/dl]) and her renal function was now impaired (BUN 36 mg/dL [3.5-9mg/dl], serum creatinine 1 mg/dL [0.6-1.3mg/dl], and a 24-hour urine protein was 1gm in 1900ml of urine). A repeat chest CT revealed more extensive GGO (Figure 2).

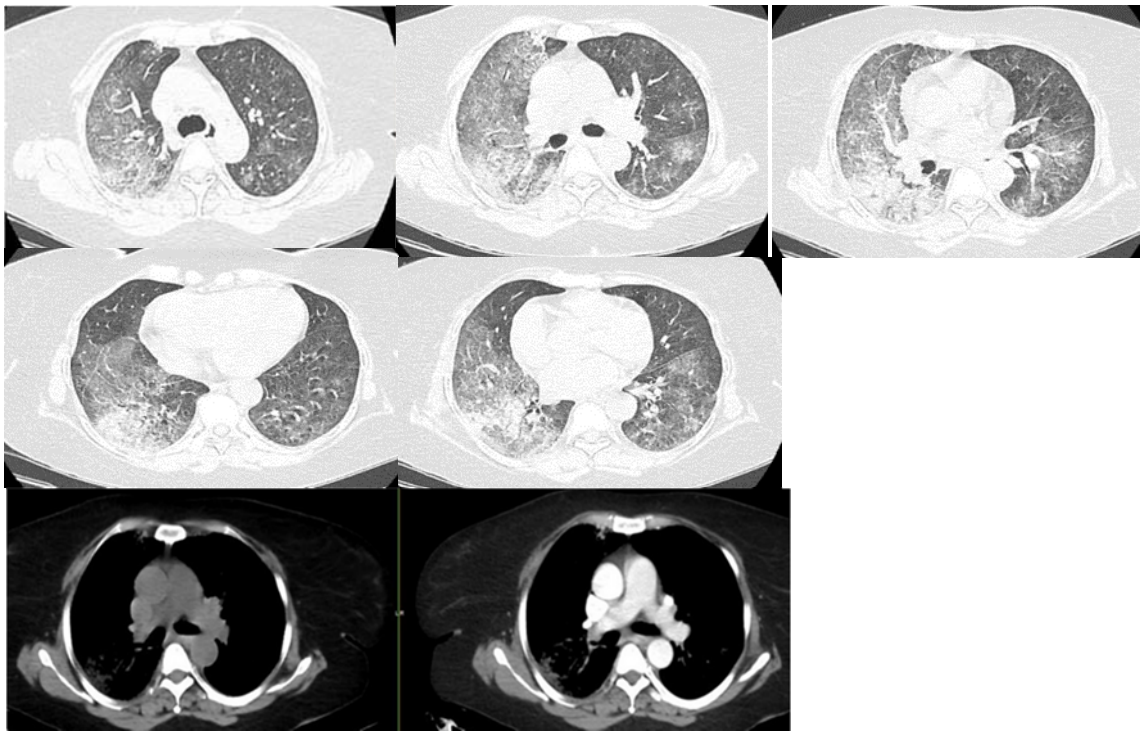

Figure 2. Axial lung and mediastinal windows of the high-resolution chest CT scan (was done at admission) showing bilateral (more diffused on the right lung and patchy on the left lung) alveolar filling and ground-glass opacification, mainly in the right lung with interval worsening from initial CT, consistent with pulmonary hemorrhage.

The patient was admitted to the medical ward with a presumptive diagnosis of PTU-induced AAV. Her PTU was stopped, and she was pulsed with methylprednisolone 1gm iv daily for 3 days and then maintained on prednisolone at 1mg/kg/day. She received 2 units of PRBC for hemoglobin of 4 mg/dl. On this treatment, her respiratory symptoms resolved and her oxygenation, renal function, and hemoglobin returned to normal.

Subsequently, cytoplasmic ANCA was positive, and both the perinuclear ANCA and antinuclear antibody (ANA) were negative, confirming the diagnosis of PTU-associated AAV. She was started on monthly IV cyclophosphamide. Currently, she is doing well; her recent chest CT showed marked clearing of her infiltrates (Figure 3). She is being evaluated for surgical management of her thyroid goiter.

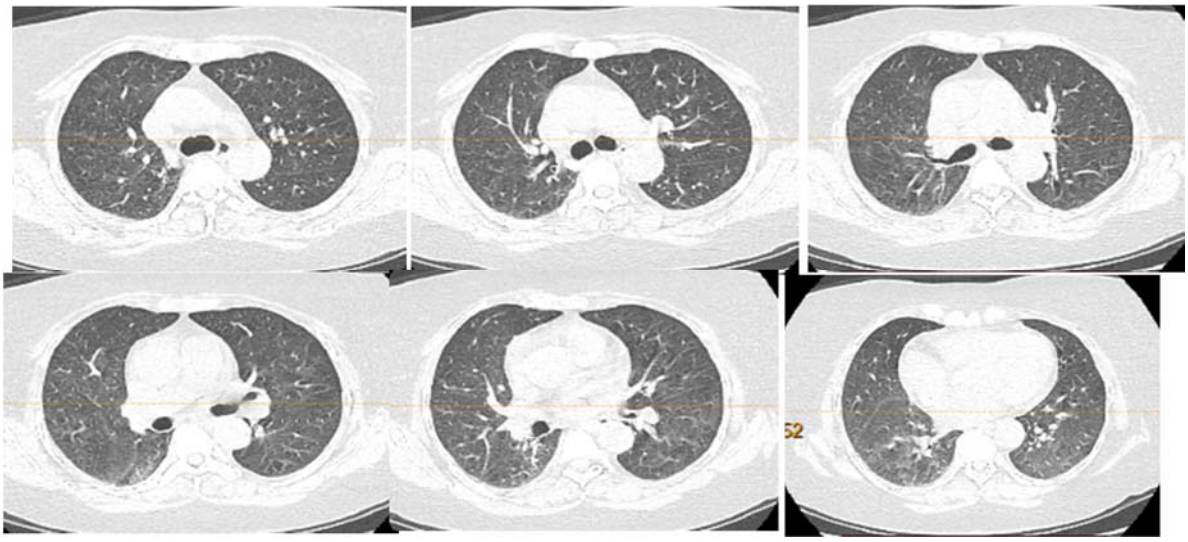

Figure 3. Axial lung windows of the high-resolution chest CT scan revealing marked resolutions of the alveolar infiltrate and ground-glass opacity after 6 weeks of PTU withdrawal, steroid, and monthly cyclophosphamide treatment, with the restoration of the lung parenchyma.

DISCUSSION

We report the first Ethiopian case of AAV associated with PTU therapy. The diagnosis was based on compatible clinical features, lack of response to antibiotics, characteristic findings on Chest CT, ANCA seropositivity, and clinical improvement after withdrawal of PTU and treatment with corticosteroids and cyclophosphamide.

Numerous case reports have previously documented the association of PTU and AAV[5-7] and several closely resemble our case. The mechanism of ANCA seropositivity and vasculitis caused by PTU has not been well defined. PTU accumulates in neutrophils and binds to and alters the myeloperoxidase antigen[8,9]. This alteration could potentially lead to the formation of autoantibodies in susceptible individuals.

For those with a mild presentation like constitutional symptoms, arthralgias/arthritis, or cutaneous vasculitis discontinuation of the culprit drug (PTU) may suffice for the necessary intervention. For cases with life-threatening or more severe disease manifestations involving lung and/or kidney involvement require treatment with high doses of glucocorticoids and cyclophosphamide or rituximab[10,11].

In conclusion, our case of PTU-associated AAV illustrates the importance of attentiveness, early identification, and aggressive treatment of this medication-induced complication.

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Conflict of Interest: There isn't any conflict of interest to report.

Consent: The patient consented to the publication of this case details.

REFERENCE

1. Stankus SJ, Johnson NT. Propylthiouracil-induced hypersensitivity vasculitis presenting as respiratory failure. Chest. 1992;102(5):1595–6.
2. Dolman KM, Gans RO, Vervaat TJ, Zevenbergen G, Maingay D, Nikkels RE, et al. Vasculitis and anti-neutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. Lancet. 1993;342 (8872):651–2.
3. Yang J, Yao LP, Dong MJ, et al. Clinical Characteristics and Outcomes of Propylthiouracil-Induced Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in Patients with Graves' Disease: A Median 38-Month Retrospective Cohort Study from a Single Institution in China. Thyroid 2017; 27:1469.
4. Noh JY, Asari T, Hamada N, Makino F, Ishikawa N, Abe Y, et al. Frequency of appearance of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) in Graves' disease patients treated with propylthiouracil and the relationship between MPO-ANCA and clinical manifestations. Clin Endocrinol. 2001;54(5):651–4.
5. Kitahara T, Hiromura K, Maezawa A, et al. Case of propylthiouracil induced vasculitis associated with anti-neutrophil cytoplasmic antibody (ANCA): review of literature. Clin Nephrol 1997; 47:336–340
6. Romas E, Henderson DR, Kirkham BW. Propylthiouracil therapy: an unusual cause of antineutrophil cytoplasmic antibody associated alveolar hemorrhage. J Rheumatol 1995; 22:803
7. Choi HK, Merkel PA, Tervaert JW, et al. Alternating antineutrophil cytoplasmic antibody specificity: drug-induced vasculitis in a patient with Wegener's granulomatosis. Arthritis Rheum 1999; 42:384–388
8. Lam DC, Lindsay RH. Accumulation of 2-[14C] propylthiouracil in human polymorphonuclear leukocytes. Biochem Pharmacol 1979; 28:2289.
9. Lee E, Hirouchi M, Hosokawa M, et al. Inactivation of peroxidases of rat bone marrow by repeated administration of propylthiouracil is accompanied by a change in the heme structure. Biochem Pharmacol 1988; 37:2151.
10. Gao Y, Chen M, Ye H, Yu F, Guo XH, Zhao MH. Long-term outcomes of patients with propylthiouracil-induced anti-neutrophil cytoplasmic auto-antibody-associated vasculitis. Rheumatology (Oxford). 2008;47(10):1515–20.
11. Zhao MH, Chen M, Gao Y, Wang HY. Propylthiouracil-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. Kidney Int. 2006;69(8):1477–81.