Agranulocytosis secondary to propylthiouracil

W. KHALIQ1, L. PONOR1, P. CHERIPALLI2, K. TANGELLA3 and Z. CHAUDHRY1

1From the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, 
2Shands Jacksonville Medical Center, Jacksonville, FL and 3College of Medicine, University of Illinois, Urbana, IL, USA

Address correspondence to: W. Khaliq, Department of Medicine, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, MFL Bldg, West Tower 6th Floor, Baltimore, MD 21224, USA. email: wkhaliq1@jhmi.edu

Case report

A 36-year-old Caucasian female presented with sore throat, malaise and fever for 5 days. She was febrile and physical examination was remarkable for moderate pharyngeal erythema and mild tonsil hypertrophy. A complete blood count (CBC) showed a white blood cell (WBC) count of 810/μl [87% lymphocytes, 8% variant lymphocytes, 5% monocytes and an absolute neutrophil count (ANC) of zero], hemoglobin (Hgb) of 9.8 gm/dl, and a platelet count of 124,000/μl. A comprehensive metabolic panel, rapid strep screen, urine analysis and chest X-ray were unremarkable. She was admitted and empirically started on ceftriaxone and levofloxacin.

The patient had no known drug allergies and a family history was significant for Graves’ disease (mother and three maternal aunts), and Factor V Leiden deficiency (father and sister). A review of the recent past medical history revealed an emergent cesarean section 4 weeks ago at 32 weeks of gestation secondary to abruptio placentae. Post-operatively the patient developed a pulmonary embolus followed by respiratory distress, tachycardia and thyrotoxicosis. During that hospitalization a CBC was unremarkable, TSH 0.005 ulU/ml, T4 16 ng/dl and T3 31.2 pg/dl, consistent with thyrotoxicosis. The patient was treated with high dose propylthiouracil, corticosteroids, beta-blockers and enoxaparin. The patient was discharged home after 2 weeks later on propylthiouracil 150 mg daily along with propranolol, warfarin and prednisone. At 1 week follow-up visit T4 was 1.92 ng/dl, T3 was within normal range and an unremarkable CBC with a WBC count of 6240/μl.

During the current admission propylthiouracil was empirically stopped. An extensive work up for agranulocytosis was unremarkable including vitamin B12, folic acid, serology for viral infections (hepatitis, HIV, CMV, EBV, parvovirus), lupus antigen and pan-cultures. A peripheral smear showed leukopenia with absent granulocytic lineages (Figure 1A), and bone marrow aspirate revealed maturation arrest in granulocytic lineages at the myelocyte/metamyelocyte stage (Figure 1B). Marked hypocellularity (10%) with panhypoplasia most pronounced in the granulocyte series was noticed on bone marrow biopsy (Figure 1C). Flow cytometry showed 4% myeloblasts, multiple immature cells and very few normal maturing myeloid cells. Once infection and malignancy were ruled out, propylthiouracil was thought to be the culprit as a diagnosis of exclusion. The patient was treated with lithium (to block thyroid hormone release) and granulocyte colony stimulating factor (G-CSF). The patient improved and discharged home after 5 days with a WBC count of 8520/μl.

Discussion

The two most commonly prescribed thionamide antithyroid drugs (ATD) in the USA are methimazole and propylthiouracil. The most frequent reaction for thionamides is rash and pruritus seen in 5% of patients. Other common adverse effects include drug fever, arthralgias, sub-maxillary and cervical lymphadenopathy. Cholestatic jaundice, lupus
like syndrome and hypergammaglobulinemia occur in few patients.\(^3\) Fatal drug reactions include agranulocytosis, neutropenia, aplastic anemia, hepatitis, jaundice, vasculitis and birth defects.\(^3\) The incidence of ATD induced agranulocytosis is 0.37% with propylthiouracil and 0.35% with methimazole.\(^4\) Mortality secondary to ATD induced agranulocytosis has been reported as high as 21.5%.\(^5\) Clinical features are usually abrupt in onset with fever or sore throat as common presenting complaints.

ATD induced agranulocytosis is unpredictable and can occur as early as 10 days after starting therapy or may be delayed for up to 3 months. It is thought to be mediated by direct drug toxicity and immunologic reactions. Propylthiouracil can readily penetrate the marrow affecting oxygen and glucose utilization of leukocytes through the oxidized metabolites.\(^6\) The immune reactions occur via IgE-mediated hypersensitivity, drug-induced IgG/IgM response and neutrophil–drug complexes.\(^7\) There are no specific diagnostic findings on bone marrow examination and a complete absence of the granulocytes is usually seen.

Although the evidence suggests that adverse effects of methimazole are dose related, no such relationship has been found for propylthiouracil.\(^8\) A greater risk of agranulocytosis has been suggested with advanced age (≥40 years) in some studies, however this relationship has not been consistent.\(^9\) The clinical importance of routine WBC and granulocyte counts in the early detection of ATD-induced agranulocytosis remains controversial and most experts argue against routine monitoring.\(^9\)

Granulocyte recovery in the peripheral blood after stopping ATD varies from a few days to 3 weeks.\(^10\) Advanced age (>65 years), sepsis and neutrophil count <100/\(\mu\)l are considered poor prognostic indicators.\(^11\) Retrospective studies have shown that treatment with G-CSF decreases the granulocyte recovery time, the rate of complications from infection, and the mortality, even in patients with asymptomatic agranulocytosis.\(^10\) However, such benefits were not shown in symptomatic agranulocytosis with a granulocyte count of <100/\(\mu\)l.\(^12\) Mean recovery time with G-CSF therapy is 6.8 days.\(^13\) Although a prospective randomized controlled trial showed no significant difference in recovery time between no treatment and G-CSF therapy, most experts recommend G-CSF therapy for ATD-induced agranulocytosis.\(^9\) After recovery use of an alternative ATD is contraindicated due to thionamide cross-reactivity,\(^9\) and alternative therapies should be considered. This case presents classic agranulocytosis (ANC of zero) that was successfully treated with G-CSF. Educating patients about common presentations of agranulocytosis can improve early detection. Currently, routine WBC count monitoring to detect agranulocytosis is not recommended. Clinicians should be aware of this peculiar adverse effect of thionamides.

**Conflict of interest:** None declared.

**References**


