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Propylthiouracil-induced agranulocytosis complicated by severe infection in a patient with Graves' disease: A case report

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Objective. Graves' disease is an autoimmune disease of the thyroid gland causing hyperthyroidism due to thyroid-stimulating hormone receptor autoantibodies. A rare, but serious complication of anti-thyroid drug therapy is agranulocytosis, a critical reduction in granulocytes leading to neutropenia and impaired infection defense.

Case report. We report a case of a 32-year-old woman with Graves' disease who developed propylthiouracil-induced agranulocytosis and pancytopenia with concurrent severe infection. The patient was treated with antibiotics and granulocyte colony-stimulating factor ultimately undergoing total thyroidectomy.

Conclusion. The case highlights a rare, but potentially life-threatening complication of anti-thyroid drug therapy. We emphasize the importance of close monitoring of patients treated with anti-thyroid drugs. Early recognition and prompt intervention are crucial as agranulocytosis is not always symptomatic. Additionally, early thyroidectomy should be considered in women of childbearing age as recurrent disease flares and therapeutic switching not only increase the risk of agranulocytosis and infection, but may also delay pregnancy.

Keywords: Graves' disease, anti-thyroid treatment, propylthiouracil, agranulocytosis, granulocyte colony-stimulating factor, thyroidectomy, potassium iodine, levothyroxine

Graves' disease is an autoimmune disease of the thyroid gland characterized by hyperthyroidism due to thyroid-stimulating hormone (TSH) receptor autoantibodies (TRAb) (Kahaly et al. 2018). Excessive thyroid hormone secretion can lead to a wide range of symptoms including tremor, heart palpitations, fatigue, sweating, weight loss, and insomnia. Diagnosis is established biochemically by the presence of TRAb and hyperthyroidism and is in some patients confirmed by a thyroid scintigraphy, which typically shows a homogeneously increased uptake in an enlarged thyroid gland.

Treatment options for Graves' disease include anti-thyroid drugs (ATDs), radioiodine therapy, and thyroidectomy. Thiamazole, also known as methimazole (MMI), is the preferred first-line ATD acting by inhibiting iodine oxidation and tyrosine coupling within the thyroid gland (Cooper 2005). Propylthiouracil (PTU), another commonly used ATD, works by inhibiting the iodination of tyrosine. Although debated, PTU is often favored during early pregnancy due to its potentially lower teratogenic risk (Liu et al. 2023).

A rare, but severe complication of ATD therapy is agranulocytosis – a critical reduction in granulocytes causing neutropenia that significantly impairs the body's ability to fight infections. PTU carries a higher risk of agranulocytosis than MMI (Noh et al.

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2024) both with a dose-dependent effect requiring careful risk-benefit assessment in clinical practice when choosing a treatment strategy.

Here, we present a case of a woman with Graves' disease who developed PTU-induced agranulocytosis and pancytopenia with a concurrent severe infection ultimately undergoing total thyroidectomy following nine days of hospitalization.

Case report

A 32-year-old woman with Graves' disease diagnosed in 2017 initially presented with mild neutropenia (1.25×10^9/L, all reference values are presented in Table 1), but no thyroid-associated ophthalmopathy (TAO). She was treated with MMI until 2019. The patient experienced a relapse of Graves' disease in 2021 with borderline neutropenia (1.53×10^9/L) that spontaneously normalized briefly requiring MMI.

The patient conceived in 2022 with initially suppressed TSH that spontaneously normalized by the second trimester. TRAb was normal during pregnancy, but slightly elevated postpartum (1.3 IU/L), why she restarted MMI (2.5 mg/day), but temporarily switched to PTU 50 mg/day upon rheumatologic recommendation due to suspected drug-induced myalgia before reverting. In January 2025, following a disease flare (TSH<0.01×10^{-3} IU/L, free thyroxine = 23 pmol/L) and a desire for pregnancy, she was started on PTU 100 mg twice daily, which was escalated to 200 mg three times daily. A few days later, the PTU dose was reduced to 150 mg three times daily, however, she was admitted to the hospital the following day.

At admission, the patient was presenting with a fever (39 °C), sore throat with tonsillar exudates and light trismus, heart palpitations, and myalgia. Initial blood work revealed borderline pancytopenia (hemoglobin 7.2 mmol/L, thrombocytes 144×10^9/L, and leucocytes 1.2×10^9/L), agranulocytosis (neutrophils 0.04×10^9/L), and elevated C-reactive protein (CRP) of 120 mg/L. PTU-induced agranulocytosis was suspected, and PTU treatment was immediately discontinued, and empiric broad-spectrum antibiotics (piperacillin/tazobactam intravenously) were initiated.

During the hospitalization, the patient developed abdominal pains prompting an ultrasound, which showed splenomegaly and findings suggestive of acalculous cholecystitis. Antibiotic coverage was escalated to include metronidazole and meropenem intravenously.

Over the following days, the patient's condition worsened, with CRP increasing to 450 mg/L, further decrease in neutrophils (0.01×10^9/L), development of mild pancytopenia (hemoglobin 6.2 mmol/L, thrombocytes 102×10^9/L, and leucocytes 0.98×10^9/L) and the addition of hypotension. A CT thorax, abdomen, and pelvis showed bilateral basal lung infiltrates, but no abdominal pathology. Spontaneous neutrophil recovery (0.30×10^9/L) was observed, but on hematologic consultation, granulocyte-colony stimulating factor (G-CSF, filgrastim 30 million units) was initiated. Splenomegaly and tonsillar

Table 1
Biochemical parameters of the patient

Component	Reference range	At admission	Peak during admission	At discharge	Postoperative
Hemoglobin (mmol/L)	7.3–9.5	7.2	6.2	7.8	NA
Leukocytes (10^9/L)	3.5–8.8	1.2	0.98	3.7	5.8
Thrombocytes (10^9/L)	165–400	144	102	293	NA
Neutrophils (10^9/L)	1.60–5.90	0.04	0.01	1.17	NA
C-reactive protein (mg/L)	<10	120	450	15	NA
TSH ($\times10^{-3}$ IU/L)	0.4–4.8	<0.01	<0.01	0.04	28.9
T3 (pmol/L)	1.4–2.8	1.6	1.6	1.9	NA
T4 (pmol/L)	70–140	165	165	NA	99
Free T4 (pmol/L)	12.0–22.0	30.2	30.2	16.6	13.4
TRAb (IU/L)	<3.09	5.69	NA	NA	NA

Abbreviations: TSH – thyroid stimulating hormone; T3 – triiodothyronine; free T4 – free thyroxine; TRAb – TSH receptor antibody. NA –not available data.

hypertrophy raised suspicion of infectious mononucleosis. However, serological testing confirmed only past Epstein-Barr virus (EBV) infection indicated by positive IgG antibodies, while all other microbiological and viral investigations yielded negative results.

The patient was hospitalized for a total of nine days. With symptomatic improvement, declining CRP and neutrophil recovery with a single dose of G-CSF, she was discharged on oral amoxicillin/clavulanic acid treatment and scheduled for outpatient follow-up. Given the risk of recurrent agranulocytosis, total thyroidectomy was recommended. Potassium iodine was administered preoperatively for 10 days to reduce thyroid vascularity and thyroid hormone levels.

One month post-admission, she underwent successful total thyroidectomy with pathology confirming Graves' disease. Postoperatively, levothyroxine replacement therapy (eltroxin 200 µg twice weekly, 100 µg five times per week) was initiated. Further follow-up of thyroid hormones was planned.

Written informed consent was obtained from the patient for this case report publication.

Discussion

Agranulocytosis is a rare, but serious adverse effect of ATD treatment occurring in approximately 0.2–0.5% of patients with Graves' disease (Vicente et al. 2017). While agranulocytosis can lead to life-threatening complications, it does not always present concurrently with infection. A large study (Noh et al. 2024), analyzing nearly 30,000 patients with Graves' disease, identified 65 cases of agranulocytosis, of which 38 patients exhibited signs of infection. Similarly, an earlier study (Tajiri et al. 1990), which followed 15,398 patients undergoing ATD treatment, has reported 55 cases of agranulocytosis with infection present in only 12 of the cases. In both studies, signs of infection included fever and sore throat similar to the case presented here.

The risk of agranulocytosis appears to be dose-dependent and varies between ATDs. While multiple retrospective studies have found no significant difference in the incidence of agranulocytosis between MMI and PTU (Vicente et al. 2017), Noh et al. (2024) have reported a higher incidence when PTU was administered. In their analysis, agranulocytosis occurred in 0.20% of patients treated with MMI (15 mg/day) and 0.81% of those receiving PTU (300 mg/day) highlighting a fourfold increased risk with PTU at equivalent potency. Both drugs also exhibited a dose-dependent increase in agranulocytosis risk. In another study by Kamitani et al. (2023), which included 12,491 patients treated with ATDs, leukopenia was observed in 1.34% of the patients, while G-CSF was administered in 0.3% of the cases. The risk of leukopenia was found to be higher with increasing doses of ATD and not the type of ATD and was most pronounced within the first 72 days of the treatment initiation.

Despite a higher risk of agranulocytosis, PTU is often preferred during pregnancy due to its lower risk of severe teratogenic effects. The 2018 European guidelines (Kahaly et al. 2018) have recommended minimizing ATD use in pregnancy due to the potential risk of birth defects. If treatment is necessary, PTU is favored over MMI. A recent meta-analysis (Liu et al. 2023) has further supported this recommendation reporting a higher incidence of congenital anomalies with MMI compared to PTU. However, switching between MMI and PTU during pregnancy did not significantly reduce the overall risk of birth defects. Notably, Noh et al. (2024) have identified five cases of agranulocytosis following a switch from MMI to PTU, three of which were due to desire for pregnancy, similar to our patient case. In contrast, no cases were observed after switching from PTU to MMI. These findings suggest that switching ATDs, particularly from MMI to PTU, should be approached with caution and accompanied by close monitoring, as agranulocytosis can occur without overt clinical symptoms but still poses a significant risk for severe infections.

Arguably, thyroidectomy should be considered earlier in women of childbearing age, as recurrent disease flares and ATD switching not only increase the risk of agranulocytosis and infection, but may also delay pregnancy. While surgical intervention carries its own risks, definitive treatment could eliminate the need for prolonged ATD therapy, thus reducing both maternal and fetal complications. The decision should be individualized weighing the risks and benefits of continued medical therapy against the potential advantages of early definitive management.

In conclusion, we present a case of agranulocytosis, a rare but serious complication of ATD therapy in a patient with Graves's disease treated with PTU to the desire for pregnancy. The condition was complicated by a concurrent severe infection requiring G-CSF treatment and ultimately total thyroidectomy. This case highlights the importance of early recognition and monitoring for agranulocytosis, especially during transitions between ATDs or when administering high-dose ATDs. Clinicians should maintain alertness for hematologic

complications, ensuring prompt intervention to minimize adverse outcomes.

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