Case Report

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Late-Onset and Recurrent Agranulocytosis During Low-Dose Methimazole Therapy in an Adolescent with Graves' Disease

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What is already known on this topic?
Methimazole is the first-line treatment for pediatric Graves' disease. Methimazole-induced agranulocytosis is rare but serious, usually occurring early in treatment, often with higher doses and symptomatic presentation. When agranulocytosis develops, methimazole is discontinued and therapy is typically switched to an alternative antithyroid drug.

What this study adds?
This case highlights asymptomatic, late-onset agranulocytosis occurring during low-dose methimazole therapy, detected solely through routine blood count monitoring. Despite an initial response, recurrent neutropenia developed, while the patient remained euthyroid despite persistent TSI positivity. The coexistence of ANA and anti-CENP-B antibodies suggests a possible autoimmune predisposition.

Abstract
Graves' disease (GD) is the most common cause of thyrotoxicosis in the pediatric population. Methimazole (MMI) is the first-line therapy; however, it may rarely cause agranulocytosis, a potentially life-threatening adverse effect. Recurrent or delayed-onset agranulocytosis presents diagnostic and therapeutic challenges due to the scarcity of reported cases. This report aims to describe a pediatric case with recurrent MMI-induced agranulocytosis and to discuss potential mechanisms and management strategies. We describe a 16-year-old female with GD who developed recurrent MMI-induced agranulocytosis. The initial episode was identified during routine monitoring at the 16th month of treatment, in the absence of clinical signs of infection. MMI was promptly discontinued, and infection precautions were implemented. Treatment with granulocyte colony-stimulating factor (G-CSF) led to rapid neutrophil recovery. However, intermittent neutropenia recurred, requiring repeated G-CSF administration. Despite persistent thyroid-stimulating immunoglobulin (TSI) positivity, the patient remained euthyroid and did not require further antithyroid therapy during 20 months of follow-up. Autoimmune serology revealed positive antinuclear antibody (ANA) and anti-centromere protein B (anti-CENP-B) antibodies, while bone marrow and genetic analyses were unremarkable. This case illustrates the complex and variable course of methimazole-induced agranulocytosis in pediatric GD. Recurrent neutropenia may occur even after initial resolution, emphasizing the need for individualized management. Persistent TSI positivity alone may not necessarily reflect ongoing disease activity or justify continued antithyroid therapy.
Keywords: thionamide; hyperthyroidism; goiter; thyroiditis; autoimmune

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Introduction
Graves' disease is the most common cause of thyrotoxicosis in the pediatric population (1). Current treatment options include antithyroid drugs (ATDs), radioactive iodine therapy, and thyroidectomy. ATDs, primarily methimazole (MMI) are commonly used as the first-line treatment for hyperthyroidism; however, the use of these agents may result in a spectrum of adverse effects, ranging from common and mild reactions such as skin rash, mild hepatic dysfunction, and arthralgia, to rare but potentially life-threatening complications including agranulocytosis, aplastic anemia, myeloperoxidase-ANCA–associated vasculitis, and hepatotoxicity (2–4). Agranulocytosis is a rare and severe complication, with a reported incidence of 0.1–1.2% (5–7).
In pediatric endocrinology literature, agranulocytosis is typically defined as an absolute neutrophil count (ANC) <500/µL, while some pediatric hematology references use a lower threshold of <100/µL (8,9). Data on the management of severe neutropenia during MMI therapy are limited. As previously reported, the first step in the management of ATDs-induced agranulocytosis is the immediate discontinuation of MMI. If an infection is present, antibiotics should be initiated, and G-CSF is commonly administered thereafter. Depending on the patient's clinical status, broad-spectrum antibiotics, corticosteroids, and other agents that promote leukocyte recovery may also be used (10). Nevertheless, the current European and American Thyroid Association guidelines do not provide explicit or standardized recommendations regarding the optimal management of this complication. Here, we report a 16-year-old female with GD who developed recurrent, late-onset MMI-induced agranulocytosis, initially detected during routine screening in the absence of infection symptoms.

Case presentation
A previously healthy 16-year-and-5-month-old female presented with complaints of restlessness and recent-onset exophthalmos. Physical examination revealed a heart rate of 110 bpm, blood pressure of 120/60 mmHg, thyromegaly, and exophthalmos. Her anthropometric measurements were as follows: weight 61.7 kg (0.57 SDS), height 171.7 cm (1.49 SDS), and BMI 20.93 kg/m² (−0.39 SDS). Baseline

laboratory results were as follows: hemoglobin 14.7 g/dL, white blood cell (WBC) 3830/μL (neutrophils 1700/μL), platelet count 235,000/μL, ALT 12 U/L, AST 11 U/L, free T3 6.78 pg/mL (normal range: 2.5–3.9), free T4 2.05 ng/mL (0.5–1.51), and TSH <0.015 mIU/L (0.38–5.33). Thyroid autoantibody testing showed anti-thyroid peroxidase >1300 IU/mL (<60), and thyroid-stimulating immunoglobulin (TSI) 3.25 IU/L (reference range: 0–0.1), measured using the Siemens Immulite TSI assay, which is specific for stimulating TSH receptor antibodies. Thyroid ultrasonography demonstrated diffuse glandular enlargement with a pseudonodular, heterogeneous parenchymal pattern and increased vascularity, findings consistent with Graves' disease.

MMI was initiated at 0.3 mg/kg/day (2 × 10 mg) together with propranolol (1 mg/kg/day). Free T3 and free T4 levels normalized after 15 days of treatment, propranolol was discontinued, and the MMI dose was gradually tapered to 2.5 mg once daily by the second month. TSH levels returned to normal by the third month of therapy. Neutrophil counts remained between 1100–2400/μL during follow-up until the 16th month, when neutropenia (300–400/μL) was detected during routine monitoring, without any signs of infection. MMI was immediately discontinued, and infection precautions were implemented. The patient was referred to the pediatric hematology department for further evaluation. Laboratory investigations, including serum vitamin B12, folate, complement (C3, C4), and immunoglobulin levels, as well as the direct Coombs test, were all within normal limits. Treatment with granulocyte colony-stimulating factor (G-CSF) at 5 μg/kg/day was initiated, leading to an increase in neutrophil count to 4300/μL (Figure 1). Despite persistent TSI positivity (0.691 IU/L; reference 0–0.1), hyperthyroidism did not recur. Intermittent recurrence of neutropenia prompted further investigations. Bone marrow biopsy revealed normal myeloid differentiation. Fluorescence in situ hybridization (FISH) and cytogenetic analyses were unremarkable. During this period, ANA and anti-CENP-B antibodies were positive, whereas anti-histone antibody—typically associated with drug-induced lupus—was negative. Intermittent G-CSF administration was required for recurrent neutropenia, but no severe infections or mucositis developed. At the 36th month of follow-up, the patient remained euthyroid [free T3 3.59 pg/mL (2.5–3.9), free T4 1.33 ng/dL (0.98–1.63), TSH 0.864 mU/L (0.51–4.17)], with mildly elevated TSI (0.46 IU/L). Although she remained mildly neutropenic, she was clinically asymptomatic and had not required G-CSF therapy for the past 16 months. Genetic analyses for chronic or congenital neutropenia revealed normal results. Informed consent for publication was obtained from patient.

Discussion

We report a 16-year-old girl who developed late-onset agranulocytosis while receiving a low daily dose of methimazole. She was asymptomatic at the time of detection, and although neutropenia initially responded to G-CSF therapy, it recurred intermittently during follow-up. After discontinuation of methimazole, the patient remained euthyroid despite persistent TSI positivity, and ANA and anti-CENP-B antibodies were also detected.

Agranulocytosis is a serious adverse effect of antithyroid drugs and requires a multidisciplinary approach. Although data on its prevalence in children are limited, it is considered a rare complication. In 95% of cases, agranulocytosis develops within the first 100 days of treatment; however, delayed onset has been reported as late as day 1344 (11). In adults, methimazole-induced agranulocytosis is generally dose dependent and rarely occurs at low daily doses (e.g., 5–10 mg/day) (6,12). Interestingly, agranulocytosis occurred both unusually late and under low-dose MMI therapy in our patient. In a previous case report, agranulocytosis also developed at the 18th month of treatment in a 6-year-old child, but the patient was receiving a higher daily dose of methimazole (20 mg/day) (13).

In adolescents and adults, agranulocytosis most often presents with isolated fever and/or sore throat (14), although severe cases such as septic shock have also been reported (15). The European Thyroid Association recommends routine monitoring if the neutrophil count is between 0.5 and 1.0 $\times 10^9$/L, whereas the American Thyroid Association does not advise routine white blood cell monitoring in patients treated with methimazole, as the onset of agranulocytosis is typically abrupt and symptomatic (2,3). However, our patient's asymptomatic presentation was an uncommon clinical feature. In a previously reported case of a patient with Graves' disease who developed pancytopenia and thyroid storm during sepsis, regular CBC monitoring allowed clinicians to recognize that the cytopenia was sepsis-related rather than methimazole-induced, enabling the continuation of methimazole therapy (16). In a related large case series, continuation of antithyroid drug therapy during the asymptomatic phase of agranulocytosis was reported to contribute to progression of this potentially fatal complication. However, when appropriate prophylactic measures were initiated immediately upon detection, approximately two-thirds of patients remained free of infectious symptoms (27). In light of these findings, although current guidelines do not recommend routine complete blood count monitoring as a universal screening strategy, early detection during the asymptomatic phase may help prevent severe outcomes. Regular hematologic monitoring may facilitate recognition of clinically silent cases and support timely intervention before life-threatening complications develop.

There are differing views regarding the use of G-CSF in antithyroid drug–induced agranulocytosis. The American Thyroid Association neither recommends nor opposes its use (2), and the American Society of Clinical Oncology does not support routine administration in afebrile neutropenia, reserving it for high-risk febrile cases (26). Nevertheless, a systematic review and meta-analysis demonstrated that G-CSF significantly shortens recovery time in antithyroid drug–induced agranulocytosis (17).

In this context, serial complete blood count monitoring in our patient revealed a progressive and unpredictable decline in neutrophil counts. Despite six days of observation after methimazole discontinuation, neutrophil levels continued to decrease (Figure 1). Given the patient's regular school attendance and ongoing exposure to crowded environments, together with multidisciplinary evaluation involving pediatric hematology, the risk of further deterioration was considered clinically significant.

Previous data indicate that G-CSF does not provide benefit when the absolute neutrophil count falls below 100/μL (12), and infection risk at this threshold becomes nearly inevitable (15). To avoid reaching this high-risk stage, and considering the potential clinical and medico-legal consequences of severe infection, early intervention was preferred.

Although reports describing G-CSF use in asymptomatic patients are limited, the large case series (12) demonstrated that asymptomatic patients had higher neutrophil counts at the time of agranulocytosis detection compared to symptomatic patients and experienced shorter recovery times. These findings suggest that earlier intervention in clinically silent cases may be associated with a more favorable hematologic response. In our patient, a prompt response to G-CSF was anticipated; however, the clinical course did not follow the expected pattern.Consistent with previous reports, agranulocytosis resolved within the first days of G-CSF treatment; however, it recurred intermittently during follow-up, suggesting partial treatment failure. Evidence regarding recurrence after G-CSF therapy is scarce. In one study, transient neutropenia occurred in two patients, but no recurrent cases were described (7). To our knowledge, prolonged intermittent recurrence following initial G-CSF response appears to be uncommon, making the present case clinically noteworthy.

The exact mechanism of methimazole-induced agranulocytosis remains unclear, though both antibody-mediated immune destruction and direct bone marrow toxicity have been proposed (10). In a large retrospective cohort of 50,385 patients with Graves' disease, no specific clinical risk factors were identified for the development of agranulocytosis (7). Conversely, genetic predispositions have been implicated. Certain HLA genotypes, such as HLA-B38:02 and HLA-DRB108:03 in Chinese populations, and HLA-B27:05 with other chromosome 6 SNPs in white Europeans, have been associated with an increased risk (18-20). In the Japanese population, HLA-B39:01:01 has been reported as a novel risk factor (21), and polymorphisms in the KLRC4-KLRK1 gene have also been linked to both susceptibility and progression (22). Genetic analyses in our patient revealed no significant findings.

Another noteworthy finding was the presence of ANA and anti-CENP-B antibodies, suggesting a possible autoimmune component. Approximately 17% of patients with Graves' disease have a coexisting autoimmune disorder, including vitiligo, autoimmune gastritis, rheumatoid arthritis, celiac disease, type 1 diabetes, systemic lupus erythematosus, or Sjögren's syndrome (23). This absence of identifiable

genetic susceptibility, combined with the presence of autoantibodies, may indicate that the pathogenesis in this case reflects an underlying immune dysregulation rather than a single genetic predisposition.

In pediatric patients with MMI-induced agranulocytosis, medical management of thyrotoxicosis before definitive therapy may involve β-blockers, inorganic iodine, glucocorticoids, bile acid sequestrants, lithium carbonate, and plasmapheresis (17,24,25). Our patient was euthyroid at the time MMI was discontinued, although TSI positivity persisted. Despite this, she was successfully monitored without resuming antithyroid therapy. These findings indicate that TSI positivity does not always correspond to active hyperthyroidism.
The major strengths of this report include detailed clinical characterization, long-term follow-up, and comprehensive evaluation of possible contributing factors, including genetic and autoimmune analyses. The recurrence of neutropenia during G-CSF therapy and the coexistence of ANA and anti-CENP-B antibodies add to the uniqueness of this case. However, the main limitation is that the findings are derived from a single patient, which limits generalizability. Moreover, the underlying mechanism of recurrent neutropenia could not be elucidated. Nevertheless, this case provides valuable insight into the variable clinical course of methimazole-induced agranulocytosis in pediatric patients.

Conclusion

Severe neutropenia during antithyroid therapy may present late, persist, and be challenging to manage. TSI positivity does not always reflect an ongoing risk of hyperthyroidism. Determining the underlying etiology of neutropenia in patients with Graves' disease may not be straightforward, and further investigation into potential underlying pathophysiological mechanisms is warranted.

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Figure 1: Trend of neutrophil count and effect of G-CSF administrations following MMI-induced agranulocytosis (Day 0).