

## Case Presentation

# Delayed Methimazole-Induced Agranulocytosis in a 6 Year Old Patient with Graves' Disease

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## Abstract

Agranulocytosis is a rare adverse reaction associated with Methimazole (MMI) therapy. It usually develops within the first 90 days of treatment. Although delayed development of agranulocytosis beyond this timeline has been documented in adults, very few children have been reported with this presentation. We describe a 6 year old patient on MMI therapy who developed agranulocytosis 18 months after the start of therapy. This is not only the youngest patient reported in literature but also a patient who developed this serious adverse reaction on stable MMI therapy well beyond the typical timeline.

**Keywords:** Graves'; Hyperthyroidism; Methimazole; Delayed agranulocytosis; Absolute neutrophil count

## Abbreviations

MMI: Methimazole; TSH: Thyroid-Stimulating Hormone; TSIg: Thyroid-Stimulating Immunoglobulin's; TBII: TSH Binding Inhibitor Immunoglobulin's; ANC: Absolute Neutrophil Count; GD: Graves' Disease; EBV: Epstein Barr Virus; CMV: Cytomegalovirus; TSHR auto-antibodies: TSH receptor antibodies; RAI: Radioactive Iodine; PTU: Propylthiouracil; FAERS: FDA Adverse Effects Reporting System; G-CSF: Granulocyte-Colony Stimulating Factor

## Case Presentation

The patient initially presented at age 5 to an outside hospital with a 1-week history of palpitations and chest pains. Physical examination revealed hypertension, tachycardia, tongue fasciculation's, and peripheral tremor. Initial testing confirmed primary hyperthyroidism with elevated free T4 level of 5.32 ng/mL (0.78-2.49) and suppressed TSH at <0.015  $\mu$ IU/mL (0.460-8.100). TSIg and TBII were elevated at 359% (<140%) and 63.4% ( $\leq$ 16%), respectively. Additional testing revealed normal ANC and liver transaminase levels. She was diagnosed with GD by an outside pediatric endocrinologist and started on a beta blocker for symptomatic relief and on MMI at an initial dose of 5 mg daily (~0.25 mg/kg/day). This dose was raised over a 4 month period to 20 mg daily (~1 mg/kg/day). She continued on this dose with optimal thyroid function control. Her family transferred care to our practice at age 5½. At this time, they denied prior symptoms of agranulocytosis, including unexplained fever, sore throat, and/or mouth sores. Subsequent routine testing every 3-4 months revealed normal ANC between 1000 and 3300 cells/ $\mu$ L.

At a routine visit at age 6½ years, her family reported a 4-day history of a sore throat associated with 2 painful lesions on her tongue and intermittent fevers. Blood testing revealed agranulocytosis with ANC of 0 cells/ $\mu$ L and MMI was immediately discontinued. She was admitted to the hospital for empiric antibiotic treatment. Her fevers resolved after day one of admission. Her ANC remained at 0 cells/ $\mu$ L for 5 days after discontinuing MMI and increased on day 6 to 100 cells/ $\mu$ L.

All inpatient testing was negative, including blood, urine, and throat cultures, and cultures of tongue lesions for herpes simplex virus 1 and 2. Testing for serum granulocyte antibodies, and IgM testing for EBV, parvovirus B19, and CMV were negative. Follow-up outpatient testing off MMI for 13 days showed an improved ANC of 900 cells/ $\mu$ L. MMI-induced agranulocytosis was diagnosed based on negative testing for other common viral causes of agranulocytosis, and improvement in ANC after discontinuation of MMI therapy.

## Discussion

GD is the most common cause of hyperthyroidism in the pediatric population [1]. GD generally presents as thyrotoxicosis, with a firm, nontender goiter, ophthalmopathy, peripheral tremor, tongue fasciculation's, tachycardia, and/or hypertension on examination [2]. Diagnostic testing relies on confirmation of hyperthyroidism with elevated thyroid hormone and suppressed TSH levels, and GD by identification of TSHR autoantibody, namely TSIg and TBII [3].

MMI is the standard of treatment for pediatric GD [2] with the goal of reaching a biochemical euthyroid state. RAI and thyroidectomy are typically reserved for children who do not achieve sustained remission on MMI and/or develop major side effects on MMI [1].

PTU was previously used until 2010 in the United States when the Food and Drug Administration issued a black box warning against its use in children [4]. This was based on reports of serious hepatotoxic effects of PTU in the pediatric population [5] and that 30% of PTU-related liver transplants between 1990 and 2007 were performed in children [5,6,7]. Furthermore, studies showed serial monitoring of transaminase levels was ineffective since PTU-induced hepatic injury had an insidious onset [5,7]. These studies suggested that PTU was both specifically toxic in children and unpredictable with screening.

Although MMI is now the drug of choice, side effects are associated with this therapy.

Minor effects, such as urticaria and arthralgia, affect up to 17% of children on MMI therapy [8]. Major side effects are agranulocytosis,

hepatotoxicity, and Stevens-Johnson syndrome [8]. Agranulocytosis, defined as ANC of less than or equal to 500 cells/ $\mu$ L [9,10]. Typically presents with fever, sore throat, and/or mouth sores [9]. The mechanism behind MMI-induced agranulocytosis is not fully understood, but thought to be the result of many factors, including direct drug toxicity and immune-mediated destruction of mature granulocytes [9].

Although rare, the exact incidence of agranulocytosis specifically due to MMI in pediatrics is unknown. Incidence of agranulocytosis due to either MMI or PTU in the pediatric GD population ranges between 0.1% to 0.2% [9]. We reviewed data from the FAERS, a database of adverse event and medication error reports submitted to the FDA. Our review of all MMI-induced agranulocytosis cases submitted over 15 years unfortunately found incomplete information with crucial missing data including patient age, MMI dose, and treatment duration.

Various studies have attempted to determine how soon agranulocytosis develops after initiation of MMI. It most commonly occurs within 6 months of starting therapy [7] with peak onset within 3 months of initiation [2]. However, 4% of children have been reported to develop adverse events including agranulocytosis, much later at 18 months [11].

MMI-induced agranulocytosis maybe dose-dependent [2]. However, extensive review of literature revealed a paucity of data on the effect of MMI dose on development of agranulocytosis, particularly in the pediatric population. Takata et al., demonstrated a statistically significant 0.6% higher prevalence of agranulocytosis in a cohort of both adult and pediatric patients treated with 30 mg MMI daily compared to 15 mg daily [11]. However, the results were not stratified according to age.

Our literature review could only identify one study by Minamitani et al. investigating dose-dependency of MMI-induced agranulocytosis in pediatric patients. In this retrospective review of 16 patients with a median age of 13 years, the median time of agranulocytosis onset on 7.5-10 mg of MMI daily was 282 days after the start of therapy. In contrast, patients on higher doses of 20-25 mg and 30-45 mg daily had shorter median onsets of 78 days and 35 days, respectively [9]. Additional studies with larger numbers of patients are necessary to assess true dose dependency of agranulocytosis.

The first step in treating MMI-induced agranulocytosis is immediate discontinuation of the drug. Since many studies have established a significant cross-reactivity between MMI and PTU, the use of this alternative anti-thyroid drug is contraindicated [9]. Initiation of intravenous broad spectrum antibiotics to cover Gram positive and negative, and anaerobic organisms is recommended, especially if the presentation includes fevers [12]. Although G-CSF therapy has been recommended to increase ANC and shorten recovery time, multiple studies have shown inconsistent results [13,14].

Alternatives to MMI therapy include RAI with 131I, and thyroidectomy [11]. Both aim to leave the patient in a chronic hypothyroid state requiring exogenous thyroid hormone replacement. Increased risk of thyroid malignancy is a concern of RAI therapy in pediatric GD. However, outcomes of over 1200 children

and adolescents treated with appropriate high doses of 131I for GD followed from less than 5 to 15 years, with some for more than 20, did not reveal increased risk of thyroid malignancy [15]. Another study by Read et al. with the longest follow-up of children treated with 131I of more than 100 patients followed for nearly 40 years after receiving treatment did not show any adverse events or deaths that could be attributed to 131I therapy [16].

The oldest form of curative therapy in GD is thyroidectomy surgery [17]. When performed by an experienced pediatric surgeon at a high volume center, short and long-term complication rates including hypoparathyroidism and recurrent laryngeal nerve injury are very low [17].

## Conclusion

This case is the first reported of a patient with GD as young as age 6 years developing agranulocytosis after 18 months on stable MMI therapy. Review of literature showed inconclusive data on MMI-induced agranulocytosis incidence in pediatrics, and on dose and time-dependency. Furthermore, as the clinical presentation of agranulocytosis can mimic common disease presentations, a high index of suspicion must be maintained in all patients on MMI, even those outside the expected dose or age range. Lastly, we encourage all pediatric and adult endocrinologists to diligently utilize the FAERS reporting system to collect crucial data on adverse effects of MMI therapy.

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