CASE REPORT

Increased risk for thionamide-induced agranulocytosis in elderly patients: a case presentation and literature review

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SUMMARY

Thionamides, such as methimazole and propylthiouracil, are used for the management of hyperthyroidism. Agranulocytosis is a rare adverse effect of thionamides and elderly patients are especially vulnerable. Here we discuss a case of an 80-year-old woman who developed agranulocytosis and pneumonia approximately 4 weeks after starting low dose methimazole therapy. Despite aggressive treatment with broad-spectrum antibiotics and granulocyte colony stimulating factor, she developed multiorgan failure and died. Our goals are to identify risk factors common to elderly patients and hopefully improve outcomes in this population when prescribed thionamides.

BACKGROUND

Thionamides, such as methimazole and propylthiouracil, are medications prescribed for management of hyperthyroidism. These drugs have been used for many years and are generally well tolerated. A significant adverse reaction from thionamides is agranulocytosis, and studies have shown that elderly patients are especially at risk.[1] The reasons for this are poorly understood, as there are very few studies focusing on thionamide-induced agranulocytosis in the elderly population. Here we discuss an 80-year-old woman who developed thionamide-induced agranulocytosis and died secondary to pneumonia and multiorgan failure. We have reviewed the characteristics of our patient and identified possible predisposing factors. We hope our findings will make healthcare providers extremely cautious when prescribing thionamide therapy in elderly patients, especially those who have these risk factors. We also encourage healthcare providers to consider monitoring blood tests and including family members when discussing thionamide therapy with elderly patients.

CASE PRESENTATION

An 80-year-old Hispanic woman with a past medical history of diabetes, hypertension, stroke and Alzheimer's disease was brought to the emergency room by her family complaining of new onset pleuritic chest pain, generalised malaise, and shortness of breath, cough and low grade fevers for approximately 5 days. About 1 month prior to this presentation, she had been seen by her primary care provider with complaints of unintentional weight loss, depression and insomnia. Her thyroid stimulating hormone was suppressed consistent with hyperthyroidism, and she had been started on methimazole 10 mg daily.

In the emergency room, her vital signs revealed a temperature of 100.5°F, heart rate of 103 beats per minute, blood pressure of 90/47 mm Hg and respiratory rate of 24 breaths per minute. Her pulmonary exam was remarkable for bilateral rales. Her outpatient medications included alprazolam, memantine, metformin, valsartan, hydrochlorothiazide, dronabinol, tolterodine and clopidogrel. Other than methimazole, no new prescription or over-the-counter medications had been introduced in the past month. Her past surgical history was significant for bilateral knee replacement. There was no history of smoking and alcohol use, and family history was unremarkable.

Admission blood work revealed a leucocyte count of 0.4×10^9/L and an absolute neutrophil count of 0 (figure 1). She also had evidence of acute renal insufficiency with an elevated creatinine of 1.3 mg/dL. Methimazole was held and neutropenia precautions were instituted. Her initial chest X-ray (figure 2) was unremarkable, but a follow-up contrast tomography of the chest performed a few days later revealed bilateral hazy infiltrates and patchy nodular consolidations consistent with bilateral pneumonia (figure 3). Broad-spectrum antibiotics and granulocyte colony stimulating factor (G-CSF) were initiated with resolution of her neutropenia and agranulocytosis within 5 days. However, despite aggressive management, the patient had an unfortunate hospital course complicated by pulmonary distress, cardiac arrhythmias and multiorgan failure which led to her death.

DISCUSSION

Methimazole and propylthiouracil are medications commonly used for treatment of hyperthyroidism and are collectively known as thionamides. They inhibit thyroid hormone synthesis by interfering with iodination of tyrosine residues in thyroglobulin. They are associated with a variety of minor side effects such as skin rash, arthralgias and gastrointestinal upset. Choosing which one to use is usually a matter of personal preference, although methimazole is frequently preferred as it has a longer half-life, is more potent and is associated with less hepatotoxicity.[2]

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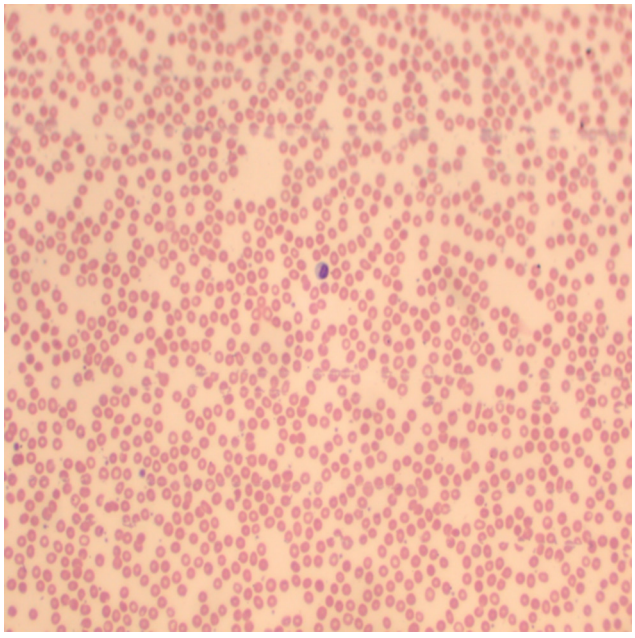

Figure 1 Peripheral blood film demonstrating agranulocytosis (Wright's stain 400×).

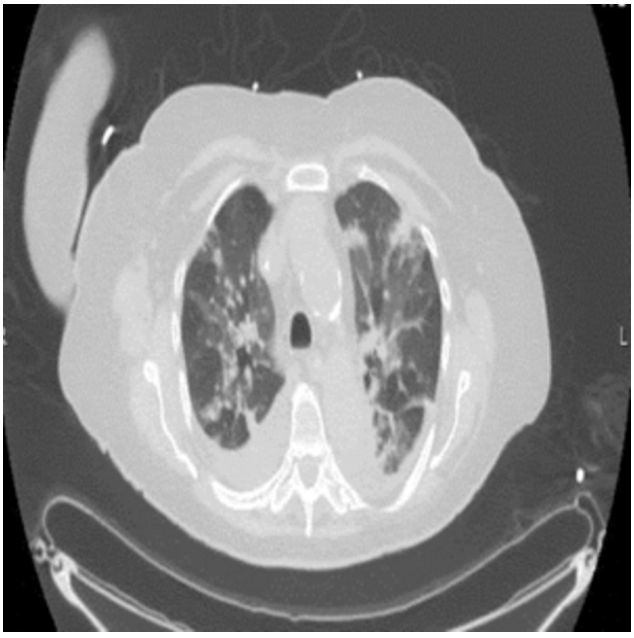

Figure 3 CT of chest showing bilateral pulmonary infiltrates and consolidations indicative of bilateral pneumonia.

Agranulocytosis is one of the most feared complications of thionamide therapy. Fortunately, it is rare, occurring in less than 1% of patients; approximately 0.4% of patients on propylthiouracil and 0.3% of patients on methimazole.[3] The exact mechanisms are unknown, but it is thought to be autoimmune-mediated, as affected patients often develop antibodies against granulocytes. Direct bone marrow toxicity from the drug has also been considered as a potential cause. Agranulocytosis may be asymptomatic, but is often accompanied by fever and sore throat. So, patients must be instructed to discontinue their thionamides and contact their healthcare provider immediately if they develop such symptoms. Agranulocytosis from thionamides usually occur within the first 90 days of treatment, but it can occur even a year or more after starting these medications.[3 4]

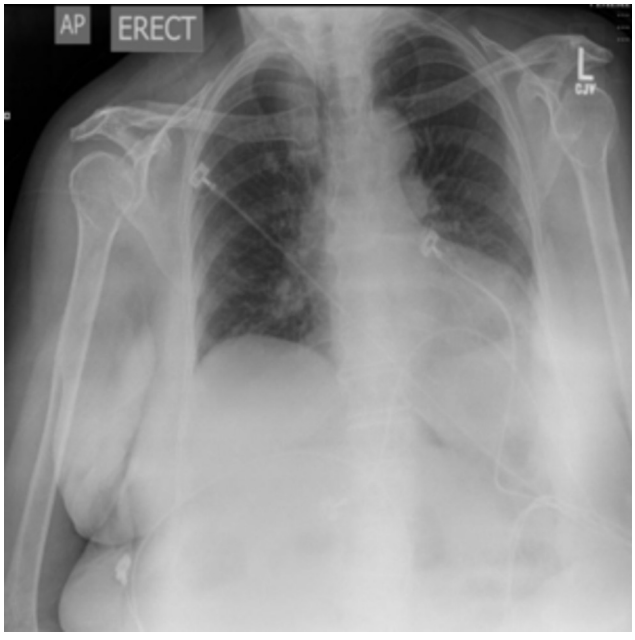

Figure 2 Chest X-ray showing no infiltrates or consolidation at the time of admission.

Elderly patients have been found to be particularly vulnerable to developing agranulocytosis from thionamides. One study demonstrated a sixfold increased risk of developing thionamide-induced agranulocytosis when patients were >40 years of age.[5] Another study found that patients who developed drug-induced agranulocytosis, in which 15% of cases were due to thionamides, and who were >60 years of age had increased mortality rates.[5 6] We offer explanations for these observations and discuss how they pertained to our patient.

One possibility may be impaired drug metabolism in older patients. Interestingly, the risk for agranulocytosis with propylthiouruacil is not dose-related, but is dose-related with methimazole. Retrospective studies have consistently demonstrated that the incidence of agranulocytosis is much less likely to occur when methimazole doses prescribed are below 15 mg daily. These data strongly advocate the use of low dose therapy as initial treatment and monitoring the patients' response before escalating the methamizole dose.[7 8]

Our patient was started on dosing consistent with these studies' recommendations, 10 mg daily, and still developed agranulocytosis. It is well established that the ageing process is characterised by changes in body composition, and hepatic and renal functions, leading to reduced clearance of medications and increased sensitivity to drugs.[9] So, it is likely that age-related medication metabolism had a role in the development of thionamide-induced agranulocytosis in our patient, despite using the recommended low dose therapy. Perhaps had she started an even lower dose such as 5 mg daily, her risk for thionamide-induced agranulocytosis may have been reduced.

Polypharmacy, the use of multiple concurrent medications may also put elderly patients at risk for agranulocytosis. A large retrospective study of over 4000 patients found female gender and polypharmacy, specifically more than five medications daily, were significantly correlated with adverse drug reactions.[10]

The specific relationship between polypharmacy and agranulocytosis while on thionamides has not been reported. However, a study specifically looking at all-cause drug-induced agranulocytosis in elderly patients also found the use of five or more medications was a predisposing factor.[6] In addition, studies and case reports have demonstrated that autonomic, anti-infective and gastrointestinal medications were associated with neutropenia when co-prescribed with clozapine, an atypical antipsychotic medication also associated with agranulocytosis.[11 12]

Our patient was female, had multiple comorbidities and was on more than five daily medications prior to starting methimazole. Of note, one of her prescribed medications was tolterodine, an autonomic medication used for overactive bladder management. It is therefore certainly reasonable to suspect that gender, polypharmacy and possibly even tolterodine put her at considerable risk for developing thionamide-induced agranulocytosis.

Cognitive impairment and delay in seeking medical attention may also put elderly patients at risk of agranulocytosis. Patients are advised to seek medical attention as soon as they develop symptoms suggestive of infection and agranulocytosis such as fever or sore throat, so the culprit medication can be immediately discontinued and supportive therapy started. Poor prognostic factors for survival include severity and duration of neutropenia, development of renal failure, and evidence of severe infections such as bacteria, septic shock and pneumonia.[5 13] These data suggest that mortality increases if patients have a delayed presentation, because they already have signs and symptoms consistent with severe infection.

Our patient had Alzheimer's disease and was likely unable to recognise or articulate her symptoms to her family or physician when they first occurred. Her family thought she had been ill for about 5 days but given the severity of her neutropenia, extent of pneumonia and renal insufficiency on admission, she likely developed agranulocytosis much earlier. Perhaps had she been brought to medical attention sooner, her agranulocytosis and pneumonia would have been more amenable to treatment.

Given the increased risk and poor prognosis of elderly patients developing thionamide-induced agranulocytosis, proactive interventions may be considered. Routine leucocyte count monitoring is not recommended for patients starting thionamides because agranulocytosis is rare and may occur abruptly. However, some studies suggest that leucocyte count monitoring after initiating thionamides may be appropriate, especially during the first few months of treatment, when the risk of agranulocytosis is greatest. In patients where routine leucocyte count was performed, agranulocytosis was sometimes found even when patients were asymptomatic, suggesting neutropenia may precede signs and symptoms of infection for days.[14] This advanced warning may be critical and beneficial for survival in elderly patients, especially those with cognitive disease such as our patient.

When thionamide-induced agranulocytosis does occur, the benefits of G-CSF are unclear. G-CSF is well studied and extensively used in the management of chemotherapy-induced agranulocytosis, but its use in thionamide-induced agranulocytosis is not firmly established. One study found that G-CSF therapy only significantly reduced neutropenia recovery time in patients with thionamide-induced agranulocytosis who were asymptomatic (2.3±1.9 days vs 5.4±4.3 days) or had symptoms and a leucocyte count $>0.1\times10^9$/L on presentation (5.5±3.5 days vs 9.2±4.4 days). The average age of the patients in this study was 40 years, and all patients survived.[15] Our patient was treated with G-CSF and had neutropenia recovery time of 5 days, consistent with this study's findings. However, she ultimately succumbed to her infection and multiorgan failure, which was not consistent. There is no firm evidence that G-CSF therapy improves survival from thionamide-induced agranulocytosis, and this is especially true in elderly patients. Therefore, further studies must be done to determine if elderly patients truly benefit.

When managing hyperthyroidism in elderly patients, healthcare providers must use extreme caution when prescribing thionamides. The risks and benefits of these medications must be clearly explained to the patient. If the patient is on multiple medications or has cognitive impairment, it may be prudent to involve additional family members in the discussion. Family members should be instructed to seek help immediately if the patient develops any worrisome signs or symptoms. Furthermore, initiating treatment with very low doses and monitoring the patient's leucocyte count frequently during the first few months of therapy may be beneficial and even life-saving. If agranulocytosis does occur, it remains unclear if G-CSF therapy improves mortality, especially in elderly patients, and more studies are needed.

Learning points

- Although thionamide-induced agranulocytosis is rare, elderly patients are at increased risk. If using methimazole, prescribing very low doses is advised.
- When initiating thionamides in elderly patients, the patients should be thoroughly and routinely educated about early recognition of symptoms such as fever or sore throat, so they may stop the drug immediately and promptly seek medical attention.
- If patients are on multiple medications or have cognitive impairment, family members should also be involved in the discussion, because close monitoring for changes in patients' health and rapid intervention may be critical for survival.
- Routine leucocyte count monitoring is generally not recommended while on thionamides because agranulocytosis may occur at any time. However, routine monitoring in elderly patients may be warranted.
- Granulocyte colony stimulating factor therapy may be beneficial in the treatment of thionamide-induced agranulocytosis in elderly patients, but more data are needed.

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Patient consent Obtained.

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