CASE REPORT

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Methimazole-Induced Aplastic Anemia with Concomitant Hepatitis in a Young Filipina with Graves' Disease

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Abstract

A 34-year-old female Filipino with Graves' disease on methimazole came in due to fever, sore throat and jaundice. She was initially diagnosed with methimazole-induced agranulocytosis and drug-induced liver injury. She was treated with intravenous broad-spectrum antibiotic and granulocyte colony stimulating factor. On day 4 of admission, she developed pancytopenia and was managed as methimazole-induced aplastic anemia. She was started on steroid therapy and received 1 unit of packed red blood cell. The jaundice also increased, hence, she was given ursodeoxycholic acid. On day 9 of admission, with the consideration of "lineage steal phenomenon," biopsy was done and eltrombopag was started. Patient was discharged stable at 12th hospital day. This case presents 3 rare life-threatening complications of methimazole namely: agranulocytosis, aplastic anemia and hepatitis.

Key words: anemia, aplastic, agranulocytosis, methimazole, antithyroid agents

INTRODUCTION

Antithyroid drug (ATD) therapy, exemplified by methimazole and propylthiouracil are essential for the treatment of hyperthyroidism, together with surgery and radioactive iodine.[1] However, the use of ATDs is not without risks. Antithyroid drug-induced agranulocytosis, aplastic anemia and hepatotoxicity are uncommon but potentially serious adverse events reported to occur with patients on these agents.[2] The frequency of agranulocytosis is reported to be 0.18-0.55%.[3] To date, at least 36 cases of aplastic anemia (AA) due to antithyroid drugs have been published.[4] Simultaneous occurrence of both aplastic anemia and hepatotoxicity in the same patient is extremely rare.[5] In our review of literature, this is the first case in the Philippines to report a case of methimazole-induced agranulocytosis, aplastic anemia and hepatitis that occurred 28 days after starting ATD .

CASE

A 34-year-old female Filipino, presented with a 1-month history of loose bowel movement, palpitations, anterior neck mass and weight loss. Upon consultation with a family physician, she was noted to have a low TSH level (<0.005 mIU/l; normal: 0.270-4.20) and elevated FT4 (4.87 ng/dl; normal: 0.932-1.71). She was then diagnosed with Graves' disease and she was started on methimazole 20 mg three times a day.

On the 28th day of treatment, she presented with a 3-day history of fever, sore throat and jaundice. She was febrile at 39.2°C and tachycardic at 127 beats per minute, regularly regular; with icteric sclerae and lingual frenulum. The thyroid was enlarged (Grade 2 by WHO criteria), soft, non-tender, no bruit. She had enlarged tonsils with exudates. Complete blood count showed leucopenia at 0.58 x 10^9/L with absolute neutrophil count (ANC) of 58 cells/μL and thrombocytopenia at 126 x 10^9/L. Her total, direct and indirect bilirubin were elevated at 6.90 mg/dL; 4.03 mg/dL; and 2.86 mg/dL respectively. The ALT was slightly elevated at 78 mg/dL and AST was normal at 37 mg/dL. Repeat thyroid function test showed a normal FT4 and TSH.

The patient was managed as a case of methimazole-induced agranulocytosis with concomitant hepatotoxicity and was treated with broad-spectrum antibiotic (cefepime) along with subcutaneous injection of granulocyte colony stimulating factor (G-CSF) 250 mcg/day. Methimazole was withheld.

At day 4 of hospitalization, despite treatment with GCSF, a repeat peripheral blood count demonstrated significant pancytopenia, the working impression was revised to methimazole induced aplastic anemia and transfusion of one unit of PRBC and steroid therapy (prednisone 20 mg tablet twice a day) were initiated. During this time, our patient was also noted to be persistently febrile, and antibiotic was shifted to a broader spectrum (piperacillin tazobactam).

At day 5 of hospitalization, due to progression of leucopenia, GCSF therapy was then increased to 250 mcg two times a day. During this time, there was also progression of jaundice, total bilirubin level was also repeated and showed further increase. She was subsequently started on ursodeoxycholic acid 500 mg/tab twice a day.

Due to persistence of fever and pancytopenia despite 3 days of steroid therapy and piperacillin tazobactam, prednisone was discontinued due to possibility of progression of infection.

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At day 7 of hospitalization, patient was already afebrile with less jaundice but with persistent pancytopenia. Final blood culture and sensitivity results were negative. The antibiotic regimen was then shifted to ciprofloxacin and G-CSF 250 mcg was continued two times a day.

At day 9 of hospitalization, repeat peripheral blood count showed improvement of white blood cell count though hemoglobin and platelet count were persistently low. A "lineage steal phenomenon" was considered, and a bone marrow aspiration biopsy under local anesthesia demonstrated a moderately hypocellular bone marrow for age with non-evident granulocytes and myeloid series than erythroids and megakaryocytes. The G-CSF was then decreased to once a day and patient was started on eltrombopag 25 mg/tab once a day.

Three days into eltrombopag therapy, a repeat peripheral blood count showed improvement in hemoglobin and platelet levels and normalization of white blood cell count. Repeat total bilirubin also showed decreasing trend. Our patient was then discharged with eltrombopag as home medication.

The patient was noted to have a complete recovery of all cell lines after 1 week of eltrombopag therapy. She underwent radioactive iodine therapy 2 weeks after her discharge (Table 1).

DISCUSSION

Agranulocytosis, aplastic anemia and hepatotoxicity are rare, independent and potentially life-threatening adverse effects of antithyroid drugs, including methimazole.[6]

Agranulocytosis is defined as an absolute granulocyte count of less than 500 per microliter. Its frequency is reported to be 0.18-0.55% in those receiving ATDs and 0.35% in those receiving methimazole.[3] Aplastic anemia (AA) is defined as pancytopenia with bone marrow hypocellularity secondary to severe damage to the hematopoietic cell compartment. It is more rare than agranulocytosis and to date; at least 36 cases of aplastic anemia due to antithyroid drugs have been published[2] for carbimazole, 32 for methimazole and 2 for prophythiouracil. Previously, it was reported that agranulocytosis and aplastic anemia developed in patients administered with more than 40 mg/day methimazole and that the usual interval between most cases is within 2 to 3 months after the start of therapy;[7] however, both could develop regardless of the dosage and duration of methimazole administration, even after years of continuous or intermittent treatment.[2] The occurrence is usually sudden with fever and sore throat being the earliest symptoms.[8]

Cholestasis and hepatocellular injury are the 2 types of hepatic injury reported following treatment with methimazole or carbimazole. Cholestasis is more common than hepatocellular injury. Liver toxicity is rare with an estimated frequency of 0.1 to 0.2%.[2] It has been reported in both sexes, at any age, usually developing in patients with doses ≥30 mg daily and presenting anywhere from 3 days to 5 months after methimazole initiation.[2] The typical presenting symptoms are abdominal pain, scleral icterus and dark urine. For our patient, she presented with scleral icterus and dark urine without symptom of abdominal pain.

In this case, our patient was started with 60 mg per day of methimazole, and she presented with fever, sore throat and jaundice 28 days after initiation of methimazole. Her initial peripheral blood count showed leucopenia at 0.58 x 10^9/L with ANC of 58 cells/μL. Her total bilirubin level was elevated. She was managed as methimazole-induced agranulocytosis with concomitant hepatitis.

The pathogenic mechanisms of agranulocytosis and aplastic anemia as a result of the administration of methimazole are unclear; however, direct cytotoxic effects by methimazole or autoimmune humoral reaction against myeloid precursors have been suggested.[9] The contribution of genetics to these immunogenic abnormalities that underlie drug sensitivity has also been shown in several studies in different population such as Hong Kongers, Chinese, Taiwanese, Vietnamese and European Caucasians. Among these population, HLA-B*38:02 is consistently associated

Table 1. Laboratory data of this case during admission

	Day-0	Day-1	Day-3	Day-5	Day-6	Day-7	Day-9	Day-11
Hgb (g/L)	123	105	88	96	102	95	82	87
Ht (%)	36	31	26	28	29	27	24	26
WBC (10^9/L)	0.58	0.76	1.49	0.57	0.88	0.75	3.46	8.81
Neutro (%)	10	4	14	12	4	10	17	60
Lympho (%)	84	84	66	68	88	78	59	35
Monoc (%)	2	8	10	12	7	12	23	5
Eosino (%)	2	4	10	8	1		1	
PLT (10^9/L)	126	117	96	96	70	65	24	32
ANC	58	30.4	209	67.4	35	75	588	5,286

	Day-0	Day-3	Day-5	Day-9
ALT (N: 10-40 mg/dL)	78	31	22	
AST (N: 10-42 mg/dL)	37			
Total Bilirubin (N: 0.2-1.0 mg/dL)	6.90	13.94	19.57	5.76
Direct Bilirubin (N: 0-0.2 mg/dL)	4.03			
Indirect Bilirubin (N: 0.2-0.7 mg/dL)	2.86			
Albumin (N: 3.5-5.5 g/dL)			2.30	
Alk. Phos (N: 44-147 IU/L)			194.12	

with ATD-induced agranulocytosis in Asian population while HLA-B*27:05 is associated with this adverse event in Caucasian population.[10-14]

As all patients with antithyroid drug-induced aplastic anemia have concomitant agranulocytosis, it is probable that these two side effects have common pathogenic mechanisms. For our patient, pancytopenia was preceded by agranulocytosis and occurred thirty one days after the initiation of methimazole.

The underlying mechanism for hepatotoxicity is believed to be idiosyncratic or immunologic. Liver toxicity with methimazole/carbimazole is possibly dose-dependent.[9] Methimazole/carbimazole reactive metabolites like glyoxal cause cytotoxicity of hepatocytes via the formation of reactive oxygen species, lipid peroxidation, and mitochondrial injury.[15] Hepatotoxicity usually resolves in all patients after the ATD is discontinued at variable intervals. For this case, ursodeoxycholic acid was started with consideration of its benefit which is protection against cytotoxicity caused by toxic bile salts, stimulation of hepatobiliary secretion, antioxidant activity, enhancement in glutathione levels, and the inhibition of liver cell apoptosis.[16]

Treatment starts with the identification and immediate discontinuation of the causative agent to prevent further damage. Intravenous broad-spectrum antibiotics are the mainstay of treatment, initiated soon after blood, urine and other samples are cultured. Hospitalization is usually required to monitor development and administration of intravenous antibiotics.[17] For our patient, methimazole was immediately discontinued. Intravenous broad-spectrum antibiotics were initiated soon after blood culture was obtained. Patient was hospitalized and started on G-CSF 250 μg subcutaneously once daily, and subsequently increased to 250 ug twice daily.

The use of granulocyte colony stimulating factor (G-CSF) in ATD-induced agranulocytosis has been shown to reduce the time to hematologic recovery, duration of antibiotic therapy, length of hospitalization and global cost.[18] The prognosis is generally good, with life-threatening infections and multiple organ failure being the most common cause of death.[19] Previous studies have reported a 2-20% mortality rate in antithyroid drug-induced agranulocytosis.[19]

On the 7th day of hospitalization, patient was already afebrile and jaundice was decreasing though pancytopenia persisted. The duration of drug-induced agranulocytosis and aplastic anemia has been reported to range from 4 to 56 days.[18] There is extremely limited information regarding the treatment of pancytopenia. The prognosis of antithyroid drug-induced aplastic anemia is usually related to the degree of bone marrow hypoplasia and blood pancytopenia. Analysis of the 36 published cases, revealed an overall good prognosis, with a survival rate of more than 94%, approximately 90% of patients obtain partial or complete clinical and laboratory recovery within 9 to 35 days.[7] Only 2 antithyroid drug-induced aplastic anemia deaths have been published. Human recombinant colony-stimulating factors were reported to have been used in combination with high-dose glucocorticoid therapy with good result.[7] In cases of severe aplastic anemia, erythrocyte and platelet transfusion is required. Adjuvant therapies such as antithymocite globulin (ATG) in combination with cyclosporine have been used in a patient with methimazole-inducted aplastic anemia.[6]

On the 9th day of hospitalization, absolute granulocyte count improved; however, there was subsequent progression of anemia and thrombocytopenia, hence lineage steal phenomenon / stem cell steal phenomenon was considered. It is a concept that is proposed based on evidence in animals that megakaryocyte, myeloid and erythroid cell lineages share a common progenitor cell; and therefore, an increase in one precursor may lead the pluripotent stem cells to evolve toward one's lineage, resulting in a decreased number of other cell lineage precursors and subsequently, mature cells.[20,21]

The patient was then started on eltrombopag. Eltrombopag is a small-molecule-thrombopoietin (TPO) receptor agonist that interacts with human TPO receptor transmembrane domain of human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. It received FDA breakthrough treatment designation in February 2014 for patients with aplastic anemia for which immunosuppression has not been successful.[22] In 2017, the NIH made eltrombopag a standard of care in aplastic anemia.[23] It has been shown to produce a trilineage hematopoiesis in some patients with aplastic anemia, resulting in increased platelet counts, along with red and white blood cell.[24] In our patient, an improvement in hemoglobin, white blood cell and platelet was noted on day 3 of eltrombopag therapy.

In cases of ATD-induced agranulocytosis and aplastic anemia, surgery or radioactive iodine seems to be an effective alternative treatment option. In fact, radioactive iodine has a success rate of 88.8% after treatment.[8] Intake of other antithyroid drugs such as carbimazole and propylthiouracil may have a cross reaction in 15.2% of patients, and therefore is contraindicated.[3]

This case underscores the importance of timely detection and recognition of these rare but dangerous side effects associated with methimazole, as well as the institution of proper therapeutic management to prevent mortality and morbidity. Physicians prescribing this drug should be aware of these potential complications that can occur at any time irrespective of age, duration of use, and methimazole dose at the first or subsequent exposure. The dose of methimazole should be commensurate with the degree of thyrotoxicosis, and a recommendation for methimazole dosing can be found in the American Thyroid Association guidelines for the management of hyperthyroidism by Ross et al. In this case, with a free T4 of 4.87 ng/dL, a dose of 30 mg a day would be appropriate, rather than 60 mg a day which was prescribed.[25] This is also why patient education at the time of methimazole initiation must not be underestimated and structured programs should be implemented. Patients should be routinely educated about the symptoms associated with these side effects and advised to immediately seek medical attention should they experience such symptoms. For patients who present with neutropenia, the offending agent should be promptly discontinued and all ATDs subsequently avoided.

CONCLUSION

Antithyroid drugs, specifically methimazole, is the first line therapy for hyperthyroidism but its use is not without any risk. Rare and life-threatening complications (<1%) include agranulocytosis, aplastic anemia and hepatitis. These complications usually occur within 2 to 3 months of therapy and they can occur with any dose of methimazole but is more frequent with larger doses (more than 40 mg/day). In this case, the dose of methimazole prescribed to the patient was probably excessive. Immediate discontinuation of the drug should be done once complications are identified. Intravenous broad-spectrum antibiotics are the mainstay of treatment for agranulocytosis. Administration of G-CSF has been shown to reduce time to hematologic recovery, duration of antibiotic therapy, length of hospitalization and cost. Though treatment with eltrombopag for drug-induced aplastic anemia is less clear, it was considered because the patient was refractory to the administration of G-CSF, and it has proven its benefit in this case.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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