Unexpected outcome (positive or negative) including adverse drug reactions

Successful treatment of methimazole-induced severe aplastic anaemia in a diabetic patient with other co-morbidities

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Summary

A 55-year-old Filipina with Grave's disease, diabetes, hypertension, bronchial asthma, Parkinson's disease and a history of adverse drug reaction to penicillin consulted due to high-grade fever and sore throat. Patient was diagnosed with aplastic anaemia secondary to methimazole and was treated with high-dose granulocyte colony stimulating factor, thrombopoietin and mesterolone. Antibiotics used included levofloxacin, clindamycin, amikacin and fluconazole. Due to bleeding and slow recovery of blood parameters, 30 units of platelets and 7 units of packed red blood cells were transfused during her 22-day admission. This case presents a life-threatening adverse drug reaction in a patient with co-morbid conditions that complicate recovery and limit one's therapeutic options.

BACKGROUND

In spite of the established efficacy and safety of antithyroids in the treatment of hyperthyroidism, life-threatening adverse reactions do occur. Most of the major adverse reactions are haematologic and among them, agranulocytosis, defined as an absolute granulocyte count of less than 500 per μl , has been the most frequently and extensively described.¹ Aplastic anaemia (AA), defined as pancytopenia with bone marrow hypocellularity secondary to severe damage to the haematopoietic cell compartment, is less common. Only 32-methimazole-induced AA cases have been published. Most of these reported improvement with concomitant use of granulocyte colony stimulating factor (G-CSF) and corticosteroids in patients without co-morbid conditions. Our patient was successfully treated with G-CSF alone albeit at higher doses (10 mcg/kg/day, usual dose is 4 mcg/kg/day) even in a background of multiple co-morbidities and a limited choice of antibiotics due to a previous adverse drug reaction to a β -lactam antibiotic.

CASE PRESENTATION

A 55-year-old Filipina with newly diagnosed Grave's disease and treated with 40 mg/day of methimazole for 6 weeks sought consult for high-grade fever (T_{max} : 40 °C) and sore throat. Her other medical conditions and medications were: (1) diabetes for 8 years with good control (HbA1c: 6.7%); on pioglitazone 15 mg/day and glimepiride 1 mg/day; (2) hypertension; on telmisartan 40 mg+HCTZ 12.5 mg daily; (3) Parkinson's disease; on carbidopa/levodopa and (4) bronchial asthma; on salmeterol+fluticasone inhalers. She also had an adverse drug experience to penicillin which manifested as maculo-

papular rash and pruritus. A complete blood count (CBC) done 1 day before this consult showed agranulocytosis (absolute neutrophil count (ANC): 12/ μl ; WBC: $0.6 \times 10^9/\text{l}$; neutrophils: 2%; lymphocytes: 11%; haemoglobin: 108 g/l; haematocrit: 0.32; platelet: $138 \times 10^9/\text{l}$). Patient had high-grade fever (T_{max} : 39 °C), tachycardia (120 beats per minute, regular), thyromegaly (approximately 4×2 cm each lobe) and a diffusely congested oropharynx with whitish exudates. Rhonchi were noted over both lung fields. There was no exophthalmos, tremors or hyper-reflexia.

INVESTIGATIONS

Peripheral blood values on the day of admission showed: pancytopenia CBC: leucocytes: $0.48 \times 10^9/\text{l}$; neutrophils: 0.01 (ANC: 4.8/ μl); lymphocytes: 0.19; platelets: $93 \times 10^9/\text{l}$; and haemoglobin: 93 g/l. On the fourth hospital day, the white blood cell (WBC) count dropped further to $0.36 \times 10^9/\text{l}$, neutrophils to 0 and platelets to $11 \times 10^9/\text{l}$. Other laboratory findings included: markedly low reticulocyte count: 0.2%; peripheral blood smear (PBS) consistent with hypochromic, microcytic anaemia, decreased platelet count; negative direct and indirect Coomb's test, negative Ham's test and sucrose lysis test; absence of occult blood in the stool and absence of haematuria; hypoprothrombinemia (prothrombin activity: 45%), normal bleeding time and clotting time and normal liver enzymes. Sputum culture showed heavy growth of *Klebsiella pneumoniae* and *Acinetobacter baumannii* while blood culture yielded *Micrococcus luteus*. Urinary and throat cultures were negative. The chest x-ray was normal. Serum thyroid stimulating hormone was suppressed at 0.07 mIU/l (normal value (NV): 0.3–3.8 mIU/l) while serum FT4 was slightly elevated at 24.3 pmol/l (NV: 11–24 pmol/l). Initial serum blood glucose was 212 mg/dl.

Figure 1 Evolution of granulocyte count during granulocyte colony stimulating factor (G-CSF) treatment.

Figure 2 Platelet count during treatment.

DIFFERENTIAL DIAGNOSIS

The patient had severe AA as evidenced by the presence of the following: ANC of 4.8/ μ L, platelet count of 11 000/ μ L and corrected reticulocyte count of 0.12%. AA may be congenital or acquired. We considered all these acquired causes in

our older patient and these include infections (hepatitis viruses, Epstein-Barr virus, parvovirus, mycobacteria), paroxysmal nocturnal haemoglobinuria and drugs. She had no signs and symptoms of viral hepatitis (ie, right-upper quadrant pain, jaundice and hepatomegaly), and her

transaminases were normal. Since the anaemia seen in Epstein–Barr virus and parvovirus infections usually have a haemolytic component, we considered these infections less likely due to a negative Coomb's test. The absence of typical signs and symptoms (ie, chronic cough, on and off fever, weight loss) and a normal chest x-ray did not point to a mycobacterial infection. Paroxysmal nocturnal haemoglobinuria was ruled out by a negative Ham's test and sucrose lysis test.

Thus, methimazole is the probable cause of our patient's anaemia due to the chronologic relationship between intake and onset of symptoms. She had been on the other medications for years and these drugs have not been reported to cause anaemia except for glimepiride, which was likewise discontinued. Methimazole, an immunosuppressant, causes adverse haematologic effects such as agranulocytosis occurring in 0.35% of the patients taking the drug. Patients usually present with high-grade fever, sore throat and ANC of $<500/\mu\text{l}$, all of which were noted in our patient.² Rarely, methimazole can cause AA which our patient eventually developed.

TREATMENT

Methimazole was discontinued. Dexamethasone 2 mg intravenous every 6 h was given to decrease peripheral conversion of thyroxine (T4) to triiodothyronine and as an adjunct to recombinant human G-CSF. However, it was eventually discontinued after 2 days due to worsening infection. Propranolol also decreases T4 conversion and controls the adrenergic symptoms of hyperthyroidism but could not be given in a patient with asthma, instead diltiazem was used. This agent effectively lowers heart rate but unfortunately does not decrease thyroxine conversion. Intravenous non- β -lactam antibiotics specifically levofloxacin, amikacin and fluconazole were also administered and the patient was placed on reverse isolation. Insulin was used to achieve normoglycaemia.

Recombinant human G-CSF 300 mcg subcutaneous once daily was started but this was increased to 300 mcg subcutaneous twice daily on the ninth hospital day when no improvement in the peripheral blood count was seen (see figure 1). She was also transfused 30 units of platelets and 7 units of packed red blood cells (RBCs). Despite platelet transfusions and G-CSF, patient's platelet count did not improve and she started manifesting overt signs of bleeding (haemoptysis and multiple ecchymoses). Thus a single dose of thrombopoietin 15 000 μl vial subcutaneous was given on the ninth hospital day (see figure 2). Fresh frozen plasma was also given.

OUTCOME AND FOLLOW-UP

ANC improved to $1728/\mu\text{l}$ by the eighteenth hospital day (WBC: $3.2\times 10^9/\text{l}$; neutrophils: 52%; lymph: 38%; haemoglobin: 81 g/l; haematocrit: 0.258; platelet: $19\times 10^9/\text{l}$). G-CSF was then decreased to 300 mcg subcutaneous every other day. Mesterolone (Proviron) an oral androgen 25 mg/tab three tabs twice daily was started. Patient became afebrile after completion of 2 weeks of intravenous antibiotics. She was discharged on the twenty second hospital day with the following CBC: WBC: $12.26\times 10^9/\text{l}$; neutrophils: 88%; lymphocytes: 7%; haemoglobin: 104 g/l; haematocrit: 0.331; platelet: $30\times 10^9/\text{l}$. Thyroid scan done showed bilobed thromegaly with areas of relative suppression in the left lat-

eral lobe which could be an effect of prior antithyroid treatment. Patient underwent thyroid ablation using 15 mCi of radioactive iodine 11 days later. On follow-up 1.5 months after discharge her blood count showed: WBC: $5.35\times 10^9/\text{l}$; neutrophils: 55%; lymphocytes: 40%; haemoglobin: 117 g/l; haematocrit: 0.35; platelet count: $372\times 10^9/\text{l}$. The reticulocyte count improved from 0.2% to 13%.

DISCUSSION

AA is a syndrome of bone marrow failure characterised by peripheral pancytopenia and marrow hypoplasia. CBC usually shows a paucity of platelets, RBCs, granulocytes, monocytes and reticulocytes. The corrected reticulocyte count is uniformly low in AA.³ Bone marrow aspiration biopsy usually reveals bone marrow hypocellularity but was deferred in this case. Severe disease, defined by the presence of two of the three parameters: ANC: $<500/\mu\text{l}$, platelet count: $<20\,000/\mu\text{l}$ and corrected reticulocyte count: $<1\%$, were seen in our patient (ANC: $4.8/\mu\text{l}$; platelet count $11\,000/\mu\text{l}$; and corrected reticulocyte count: 0.12%).³

Only 32 cases of methimazole-induced AA have been reported to date. Due to the rarity of this condition, its pathophysiology has not been completely delineated. It has been suggested that the most likely mechanism is an autoimmune humoral reaction against myeloid stem cells rather than against mature circulating neutrophils. The same mechanism has been postulated in agranulocytosis.⁴ This is supported by the presence of bone marrow plasmacytosis in two previously reported cases of methimazole-induced AA.^{5–6} A direct toxic effect of antithyroid drugs to the bone marrow cannot be excluded, since many patients who developed the condition received moderately high doses.⁷ All reported cases of antithyroid-induced AA also had concomitant agranulocytosis. Thus, it is also possible that these two side effects have common pathogenetic mechanisms.⁴

Antithyroid-induced AA occurs more often in women (Grave's disease being more common in females) and in those who received high doses and usually within the first 6 months of treatment.⁸ Unlike agranulocytosis which is more common in older patients, the occurrence of antithyroid-induced AA is not age-related.⁴

Due to the idiosyncratic nature of these reactions, clear cut therapeutic guidelines have not yet been established. Like agranulocytosis, antithyroid-induced AA is reversible with discontinuation of the offending drug.⁹ Supportive haematologic therapy (packed RBC and platelet transfusions) as was given promptly to this patient is very important. Timely and appropriate antimicrobial therapy is also essential in the management. Since *Pseudomonas aeruginosa* is the leading cause of community acquired sepsis in patients with antithyroid drug-induced agranulocytosis,¹⁰ antimicrobial agents chosen should cover the said microorganism. In patients like ours, with a history of adverse drug experience to penicillin, the choice of antibiotics becomes limited. Antimicrobial agents with a β -lactam ring should be avoided as these agents exhibit complete cross-allergenicity with penicillin. A quinolone such as levofloxacin and aminoglycoside such as amikacin can be substituted.

Besides supportive care and treatment with broad-spectrum antibiotics, several drugs including glucocorticoids,^{11–12} G-CSF,¹² granulocyte-macrophage-CSF,¹³ androgens¹⁴ and human immunoglobulin⁵ have been tried

in severe cases. Knowing that the likely pathogenetic mechanism of methimazole-induced AA is autoimmune, glucocorticoids are usually given. Initially, our patient was given dexamethasone for the hyperthyroidism, but was later discontinued due to worsening infection and relative clinical and biochemical euthyroidism. G-CSF which acts primarily on the granulocyte late precursors and potentiates the survival and function of mature neutrophils,¹⁵ had been used with some success in several reported cases. Our patient was also given G-CSF but at a relatively higher dose (600 mcg/day) compared with the G-CSF used previously by other authors (300–480 mcg/day). It also took longer (18 days) to raise this patient's ANC to >1000/μl whereas other authors reported improvement in the ANC after approximately 1 week of G-CSF therapy. Unlike other previously reported cases, we also tried using recombinant human thrombopoietin, a thrombopoietin mimetic found to be effective in reducing surgical thrombocytopenia and bleeding based on animal studies.¹⁶ When the patient's ANC started to rise, we shifted G-CSF to mesterolone an androgenic steroid for its potential role in stimulating erythropoiesis.¹⁷ Despite reports of success associated with the use of such agents, efficacy has not been verified yet by randomised controlled trials. Whether the resolution of the AA in this and other reported cases was secondary to the administration of the above-mentioned agents or simply due to withdrawal of the offending antithyroid, still remains to be investigated.

The prognosis of antithyroid drug-induced AA is usually related to the degree of bone marrow hypoplasia and blood pancytopenia. Prognosis is good overall, with a survival rate of more than 94%; approximately 90% of patients obtain partial or complete clinical and laboratory recovery within 9 and 35 days. Deaths that occurred a few decades ago were attributed to intracranial haemorrhage in patients who were thrombocytopenic and did not receive platelet transfusion.⁹

Learning points

- ▶ Early recognition of this potentially life-threatening adverse drug reaction vital so that appropriate supportive and therapeutic measures can be promptly initiated.
- ▶ Since this adverse reaction is idiosyncratic in nature, patients should be informed of these side effects and instructed to promptly discontinue the medication and seek medical attention immediately if fever or sore throat develops.
- ▶ Once the diagnosis is established, treatment consists of immediate admission to the hospital, discontinuation of the drug, broad-spectrum antimicrobial therapy, isolation techniques and strict infectious control and supportive haemotherapy. Other modalities of treatment such as G-CSF, androgens and glucocorticoids may be beneficial.
- ▶ Randomised controlled trials should be done to investigate the efficacy of such treatment modalities in antithyroid-induced AA.

Patient consent Obtained.

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