

CASE REPORT

Necrotising laryngitis and epiglottitis in a patient with methimazole-induced agranulocytosis

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Abstract

Antithyroid drug-induced neutropenia is a rare and potentially life-threatening complication with an incidence of agranulocytosis ranging from 1-5 cases per million per year. Here we report a case of a 57-year-old female with septic shock due to necrotising laryngitis and epiglottitis as a result of methimazole-induced agranulocytosis. She was treated with antibiotics, granulocyte colony-stimulating factor, and radiological and surgical abscess drainage during a 24-day stay in the ICU. This case underlines once more the importance of patient education with the use of antithyroid drugs.

Background

Agranulocytosis is a rare and potentially life-threatening side effect of methimazole treatment. The reported incidence of agranulocytosis ranges from 1-5 cases per million per year.⁽¹⁾ A direct association with drugs is found in approximately 70% of all cases.⁽²⁾ Thionamides, antithyroid drugs, belong to the group of drugs that is most commonly associated with agranulocytosis.⁽³⁾ The definition of antithyroid drug-induced agranulocytosis is a granulocyte count of $<0.5 \times 10^9$ cells/l or a grade 4 neutropenia according to the common toxicity criteria.⁽⁴⁾ Patients usually

present with fever (92%) and sore throat (85%). Here we describe a patient with a methimazole-induced agranulocytosis complicated by necrotising laryngitis and epiglottitis.

Case report

A 57-year-old female was referred to the emergency department with stridor after a five-day history of arthralgia and progressive sore throat. Given her clinical condition, which was progressing rapidly toward septic shock, a quick nasopharyngoscopy was performed in the operating theatre after which she was intubated and transported to the ICU. The nasopharyngoscopy showed necrotising laryngitis and epiglottitis (*figure 1*).

Her medical history revealed a hemithyroidectomy (1980) due to multinodular goitre, laparoscopic cholecystectomy (2002) and a recently diagnosed hyperthyroidism (multinodular goitre) for which she started treatment with methimazole approximately three months prior to this admission. Laboratory findings demonstrated increased inflammatory parameters, acute kidney injury and acute liver failure. Remarkably, the white blood cell count was decreased (0.3×10^9 cells/l (normal range $4.0-10 \times 10^9$ cells/l)) with complete agranulocytosis 0.0×10^9 cells/l (*table 1*).

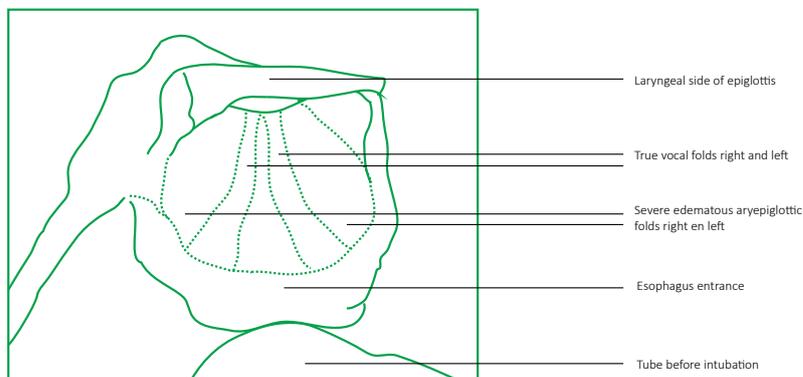
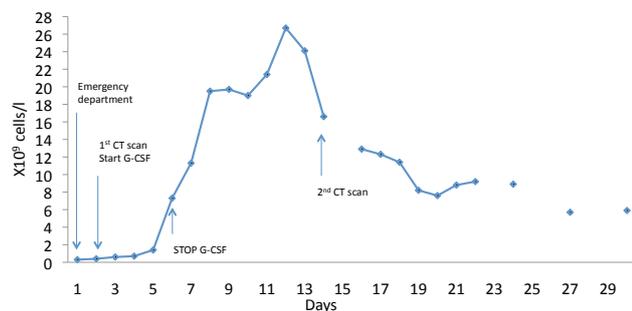


Figure 1.

Table 1. Laboratory findings at admission

		Reference
Erythrocyte sedimentation rate	>110	0-30 mm/h
C-reactive protein	286	0-8 mg/l
Red blood cell count	7.3	7.5-10 mmol/l
Haematocrit	0.36	0.35-0.45
Mean corpuscular volume	72	80-100 fl
Platelet count	245	15-400 x 10 ⁹ /l
White blood cell count	0.3	4.0-10 x 10 ⁹ /l
Neutrophils-segmented	0.0	1.5-7.5 x 10 ⁹ /l
Lymphocytes	0.3	1.0-3.5 x 10 ⁹ /l
Monocytes	0.0	0.1-1.0 x 10 ⁹ /l
Eosinophils	0.0	0.1-0.5 x 10 ⁹ /l
Basophils	0.0	0.0-0.2 x 10 ⁹ /l
Sodium	137	135-145 mmol/l
Potassium	3.2	3.5-4.8 mmol/l
Urea nitrogen	15.1	2.5-6.4 mmol/l
Creatinine	242	40-90 µmol/l
Bilirubin, total	67	0-17 µmol/l
Alkaline phosphatase	87	33-98 U/l
Gamma-glutamyltransferase	59	0-38 U/l
Alanine aminotransferase	34	0-31 U/l
Lactate dehydrogenase	319	0-247 U/l
Glucose	9.0	3.9-6.1 mmol/l

A sputum smear demonstrated *Staphylococcus aureus* and *Streptococcus pneumoniae*, and she was treated with amoxicillin-clavulanic acid (1200 mg four times a day) and clindamycin (600 mg three times a day), both intravenously. Filgrastim (5 µg/kg subcutaneously), a granulocyte colony-stimulating factor (G-CSF) was administered for five days until reconstitution of the neutrophils (figure 2).

**Figure 2.**

On day 2 of admission, a CT scan was performed ruling out a possible mastoiditis or abscess as a focus for the necrotising laryngitis. At this time, the white blood count was 0.6 x 10⁹ cells/l. Besides pansinusitis, no abnormalities were seen in the neck or thorax. During the following days, the patient's condition, and laboratory parameters improved in parallel with the neutrophil count. Although regular inspection of the larynx and epiglottis showed improvement of the necrotic tissue and epiglottitis, continuous swelling of the larynx was observed. On day 11, (leucocytes 21.4 x 10⁹ cells/l) another CT scan was performed (figure 3), demonstrating bilateral abscesses in the sternocleidomastoid muscle region.

**Figure 3.** Day 15 CT: bilateral abscess

Ultrasound-guided percutaneous abscess drainage was performed on the right side whereas a second collection (left) was drained surgically. Under empiric treatment with piperacillin and tazobactam, the patient's clinical condition improved rapidly and she was successfully extubated on day 24, seven days after abscess drainage. Another four days later she was discharged from the hospital.

Discussion

Here we present a case of methimazole-induced agranulocytosis, complicated by septic shock due to necrotising laryngitis and epiglottitis. Although treatment with G-CSF resulted in an early reconstitution of the white blood cell count, the ICU course was complicated by pyomyositis and abscess formation in the sternocleidomastoid muscle. After drainage of the abscesses, the patient recovered completely.

Drug-induced agranulocytosis

The two best-described mechanisms through which drugs induce neutropenia/agranulocytosis are a) immune-mediated destruction of circulating neutrophils and b) direct toxic effects on bone marrow granulocytic precursors. Both mechanisms seem to be mediated by reactive metabolites. The nicotinamide adenine dinucleotide phosphate-oxidase (NAPDH) oxidase/myeloperoxidase enzyme system, found in neutrophils and monocytes, is most likely responsible for oxidising specific antithyroid drugs into these reactive metabolites.^(5,6) Neutropenia or agranulocytosis generally presents in the first months after the start of treatment. In Japan, an incidence rate of 0.1-0.15% was observed in the last 30 years. Agranulocytosis was six times more common among females, and developed within 90 days after starting antithyroid drug treatment in

84.5% of patients.^(4,7,8)

Although agranulocytosis could result in severe infectious complications, standardised or frequent measurement of the absolute granulocyte count is not performed on a routine basis. This approach is not effective or cost-effective since agranulocytosis develops abruptly.⁽⁴⁾

At this moment, there is no prognostic tool to identify patients at risk for drug-induced neutropenia/agranulocytosis. Therefore patients who start treatment with antithyroid drugs are educated about the possible consequences regarding their immune system and should always contact the general practitioner in case of fever or a sore throat.^(4,9) If a patient has severe neutropenia or agranulocytosis the possible offending drug should be stopped immediately, regardless of any symptoms. After cessation of the drug, neutropenia usually resolves within 1-3 weeks.⁽⁸⁾ When agranulocytosis is associated with secondary infections, the use of G-CSF has been associated with a shorter recovery time and less use of antibiotics.⁽⁹⁾

Epiglottitis and necrotising laryngitis

Our patient initially presented with a very severe epiglottitis and necrotising laryngitis. The incidence of epiglottitis in adults is 0.6-1.9 cases per 100,000 persons annually. The incidence of epiglottitis peaks at 2-8 years and 35-39 years of age.⁽¹⁰⁾ Since the implementation of vaccination against *Haemophilus influenzae* type b (Hib) the incidence of epiglottitis has been reduced among children,⁽¹¹⁾ but has not changed for adults.⁽¹²⁾

Conclusion

Although antithyroid drug-induced agranulocytosis remains a rare complication, patient education is still essential. When severe agranulocytosis is accompanied by severe infectious complications, treatment with G-CSF has been associated with a shorter recovery time and less use of antibiotics.

Disclosure

All authors declare no conflict of interest. No funding or financial support was received.

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