Antithyroid-drug-induced agranulocytosis complicated by life-threatening infections

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Summary
Agranulocytosis is a rare complication of antithyroid drugs, and the aetiologies of community-acquired, life-threatening infections in patients taking these drugs have not previously been systematically described. Of 5653 hyperthyroid patients treated with antithyroid drugs at National Taiwan University Hospital between January 1987 and December 1997, 13 (0.23%) developed agranulocytosis with life-threatening infections. The most common presentations were fever (92%) and sore throat (85%). Initial clinical diagnoses were acute pharyngitis (46%), acute tonsillitis (38%), pneumonia (15%) and urinary tract infection (8%). Positive blood cultures from six patients yielded Pseudomonas aeruginosa (3), Escherichia coli (1), Staphylococcus aureus (1), Capnocytophaga species (1). Two patients died of uncontrolled infection, thyroid storm and multiple organ failure. Cases of antithyroid-drug-induced agranulocytosis in the English language literature are reviewed; Gram-negative bacilli, including Klebsiella pneumoniae (4 patients) and P. aeruginosa (3), were the most common pathogens in clinical isolates. Our observation and review suggest that broad-spectrum antibiotics with anti-pseudomonal activity should be given to patients with antithyroid drug-induced agranulocytosis who present with severe infection.

Introduction
Antithyroid drugs derived from thionamides, including methimazole and carbimazole, have been widely used to treat patients with hyperthyroidism since 1940s. They are convenient, effective and cheap. Side-effects of these drugs are few, and include skin rashes, urticaria, arthralgia and fever. The symptoms are usually mild and transient. Leukopenia, which may occur in untreated patients with thyrotoxicosis and in 1–5% of patients treated with antithyroid drugs, is usually benign and does not increase the risk of agranulocytosis and infection. Agranulocytosis (absolute neutrophil count, ANC < 500 × 10⁶/l) is rare, and may develop in 0.2–0.5% of patients taking antithyroid drugs. It may occur suddenly and explosively, and may be complicated by severe infections in otherwise immunocompetent patients.

The microbiology of such infectious complications has not been systematically reviewed previously. In this report, we describe 13 cases of antithyroid drug-induced agranulocytosis complicated by life-threatening sepsis, and review the reported cases in the English literature. Our findings emphasize the importance of Gram-negative bacilli, especially Pseudomonas aeruginosa, as one of several aetiologies of these infectious complications.

Methods
Between January 1987 and December 1997, all cases of hyperthyroidism at National Taiwan University Hospital were retrospectively reviewed.
using the International Classification of Diseases 9th Revision, Clinical Modification 4th edition (ICD-9-CM). Medical records of patients with thyrotoxicosis, with/without goitre (disease code number 242), combined with leukopenia/agranulocytosis (disease code number 288.0), were reviewed. Patients who developed agranulocytosis due to antithyroid drugs (thionamides or propylthiouracil) were identified and formed the basis of this study. Patients with leukopenia attributable to other drugs or medical illnesses were excluded.

A standardized case record form was used to record demographic data, thyroid diseases, concomitant medical illness, dosage and duration of the offending antithyroid drugs. Clinical presentation and sites of infection, microbiological results, treatment (including use of granulocyte colony-stimulating factor, G-CSF), duration of recovery of leukocyte count after discontinuing medication, and final outcome of patients with agranulocytosis induced by antithyroid drugs were also recorded on the form.

Agranulocytosis was defined as an absolute neutrophil count (ANC) <500 × 10⁹/l. Sepsis in these patients was defined as clinical evidence of infection plus a systemic inflammatory response to infection. This systemic response was manifested by at least two of the following three conditions: (i) oral temperature of >38 °C or <36 °C; (ii) respiratory rate of >20 breaths/min or PaCO₂ of <32 torr; (iii) heart rate of >90 beats/min.

Statistical analysis was performed using SPSS statistical software (Version 6.1.3). The non-parametric Mann-Whitney U test was used for comparison of the duration of leukocyte count recovery between patients treated with G-CSF and those without G-CSF. A p value of 0.05 or less was considered significant.

The literature was reviewed by searching MEDLINE using the index terms of neutropenia, agranulocytosis and antithyroid drugs (including propylthiouracil and thionamides). References or bibliographies cited in each article concerning antithyroid drug-induced agranulocytosis were also reviewed.

Results

There were a total of 5653 patients with hyperthyroidism who were treated with antithyroid drugs (thionamides and propylthiouracil) at National Taiwan University Hospital between January 1987 and December 1997. Thirteen (0.23%) of them developed agranulocytosis induced by antithyroid drugs, and all 13 had obvious symptoms and signs consistent with sepsis (Table 1). There were three males and 10 females, with a median age of 39 years (range 17–78 years). Three had Graves’ disease and 10 had toxic multinodular goitres. All 13 received thionamides—carbamazole or methimazole. Eleven patients received methimazole 15–30 mg per day for 16–122 days (median 42 days). The other two patients (5 and 9) received carbimazole 30 mg per day for 21 and 61 days, respectively.

The initial leukocyte count at the presentation of sepsis ranged from 240 to 1960 × 10⁹/l (median 800 × 10⁹/l) and ANC ranged from 0 to 236 × 10⁹/l (median 0/l). The presenting symptoms of the infectious complications were fever (92%), sore throat (85%), chills (38%), watery diarrhea (15%), nausea (15%), vomiting (15%), oral ulcers (15%), productive cough (15%), dysphagia (8%), headache (8%) and dysuria (8%). Initial clinical diagnoses based on the symptomatology were acute pharyngitis (46%), acute tonsillitis (38%), pneumonia (15%) and urinary tract infection (8%).

Eight of 13 patients had their causative organisms identified from blood (six patients), pus from tonsillar abscess (1) or pus of leg ulcer (1). Three of our six bacteraemia patients had positive cultures from retropharyngeal abscess (1), peritonsillar abscess (1) or urine (1) Pseudomonas aeruginosa was the most common pathogen isolated (four patients), followed by Escherichia coli (1), Klebsiella pneumoniae (1), methicillin-sensitive Staphylococcus aureus (1), and Capnocytophaga species (1). Blood cultures were positive in six patients, three of which grew P. aeruginosa.

All patients received intensive care, empirical therapy with antipseudomonal antibiotics and surgical drainage of pus. G-CSF 5 μg/kg of body weight was given to 6/13 patients. All surviving patients had recovery of ANC after discontinuation of antithyroid drugs. The time to recovery was 4–12 days (median 9 days) in patients treated with G-CSF, and 5–10 days (median 7 days) in patients treated without G-CSF (p = 0.84). Two patients died, having developed uncontrolled infection, thyroid storm and multiple organ failure.

In a search of MEDLINE for the period from 1965 to December 1997, we identified nine other patients with agranulocytosis induced by antithyroid drugs who developed community-acquired sepsis with positive microbiological results (Table 2). The clinical presentations were fever (seven patients), sore throat (4), and diarrhea (2), while clinical diagnoses were acute tonsilloharyngitis (3), colitis (2) and pneumonia (1). K. pneumoniae (3) and P. aeruginosa (2), were the most common causes of bacteraemia, followed by Enterobacter aerogenes (1), E. coli (1), S. aureus (1), and group G Streptococcus (1). The associated complications described in these patients were septic shock (2), thyroid storm (2), colonic perforation (1), retroperitoneal abscess (1), drug-induced hepatitis (1), disseminated intravascular coagulation (1), pneumonia (1) and multiple-organ
Table 1  Clinical characteristics of 13 patients with antithyroid-drug-induced agranulocytosis

| Patient | Age (years)/sex | Thyroid diseases/other medical illnesses | Antithyroid drugs/daily dose/duration | Initial leucocyte count/ANC (× 10^6/l) | Clinical symptoms | Clinical diagnosis | Complications | G-CSF usage/recovery days | Outcome | Blood cultures | Other sites of positive culture/isolate |
|---------|----------------|--|----------------------------------------|---------------------------------------|--------------------------------------|------------------|------------------|----------------|--------------------------|---------|----------------|---------------------------------------|
| 1       | 17/F           | GAD | MMZ/30 mg/61 d                         | 320/48                                | Fever, chills, sore throat           | Acute pharyngitis | Retropharyngeal abscess, septic shock | +/5           | Recovery                  | P. aeruginosa | Retropharyngeal abscess/P. aeruginosa |
| 2       | 46/F           | TMG, DM | MMZ/30 mg/27 d                      | 240/0                                | Fever, sore throat, diarrhea, vomit, nausea, productive cough | Acute tonsillitis, Pneumonia | Nil | +/10 | Died | No growth | Tonsillar abscess/K. pneumoniae |
| 3       | 27/M           | GAD | MMZ/30 mg/61 d                         | 850/0                                | Fever, sore throat, chills             | Acute tonsillitis | Nil | +/9  | Recovery | P. aeruginosa | Nil |
| 4       | 59/F           | TMG, DM | MMZ/15 mg/16 d                      | 1800/162                             | Fever, sore throat, nausea, vomit, oral ulcer | Acute pharyngitis | Nil | −/5  | Recovery | No growth | Nil |
| 5       | 44/F           | TMG | CMZ/30 mg/21 d                         | 700/42                               | Fever, sore throat                     | Acute tonsillitis | Leg ulcer due to septic emboli, DIC, septic shock | −/7           | Recovery | No growth | Leg ulcer pus/P. aeruginosa |
| 6       | 35/M           | TMG | MMZ/30 mg/35 d                         | 800/0                                | Sore throat                            | Acute pharyngitis | Nil | −/5  | Recovery | No growth | Nil |
| 7       | 39/F           | TMG | MMZ/15 mg/49 d                         | 600/0                                | Fever, sore throat                     | Acute tonsillitis | Nil | −/8  | Recovery | P. aeruginosa | Nil |
| 8       | 28/M           | TMG | MMZ/30 mg/49 d                         | 400/0                                | Fever, sore throat, headache           | Acute pharyngitis | Nil | −/7  | Recovery | Capnocytophaga spp | Nil |
| 9       | 38/F           | GAD | MMZ/30 mg/61 d                         | 1960/38                              | Fever, sore throat, oral ulcer         | Acute pharyngitis | Nil | +/4  | Recovery | No growth | Nil |
| 10      | 26/F           | TMG | MMZ/15 mg/42 d                         | 900/0                                | Fever, chills, sore throat             | Acute pharyngitis | Nil | −/10 | Recovery | No growth | Nil |
| 11      | 61/F           | TMG | MMZ/30 mg/30 d                         | 830/12                               | Fever, chills, dysuria                 | UTI | Nil | +/12 | Recovery | E. coli | Urine/E. coli |
| 12      | 78/F           | TMG, CHF | MMZ/30 mg/122 d                     | 300/0                                | Fever, diarrhea, nausea, vomit, productive cough, dyspnoea | Pneumonia | Nil | +/11 | Died | No growth | Nil |
| 13      | 46/F           | TMG | MMZ/30 mg/14 d                         | 1570/236                              | Fever, chills, sore throat             | Acute tonsillitis | Peritonsillar abscess | −/9           | Recovery | S. aureus | Peritonsillar abscess/S. aureus |

ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CMZ, carbimazole; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; GAD, Graves’ disease; G-CSF, granulocyte colony-stimulating factor; MMZ, methimazole; TMG, toxic multinodular goitre; UTI, urinary tract infection.
<table>
<thead>
<tr>
<th>Patient (reference)</th>
<th>Age (years)/sex/medical illness</th>
<th>Clinical symptoms</th>
<th>Antithyroid drugs/daily dose/duration</th>
<th>Initial WBC/ANC (×10⁹/l)</th>
<th>Clinical diagnosis</th>
<th>Complications</th>
<th>Outcome</th>
<th>Positive blood cultures</th>
<th>Other sites of positive culture/isolate</th>
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<tbody>
<tr>
<td>1 (8)</td>
<td>NM/Nil</td>
<td>NM/NM</td>
<td>NM/NM</td>
<td>NM/NM</td>
<td>NM/NM</td>
<td>NM</td>
<td>Recovery</td>
<td>S. aureus</td>
<td>Nil</td>
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<td>2 (8)</td>
<td>NM/Nil</td>
<td>Fever, chills, bloody diarrhoea</td>
<td>MMZ/30 mg/49 d</td>
<td>1100/11</td>
<td>Colitis</td>
<td>Colon perforation, retroperitoneal abscess</td>
<td>Recovery</td>
<td>P. aeruginosa</td>
<td>Nil</td>
</tr>
<tr>
<td>3 (8)</td>
<td>48/F/GAD</td>
<td>Fever, chills, bloody diarrhoea</td>
<td>MMZ/30 mg/49 d</td>
<td>1100/11</td>
<td>Colitis</td>
<td>Colon perforation, retroperitoneal abscess</td>
<td>Died</td>
<td>P. aeruginosa and K. pneumoniae</td>
<td>Nil</td>
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<td>4 (9)</td>
<td>55/F</td>
<td>Fever, sore throat</td>
<td>PTU/300 mg/44 d</td>
<td>900.0</td>
<td>NM</td>
<td>Drug-induced hepatitis</td>
<td>Recovery</td>
<td>No growth</td>
<td>Urine/K. pneumoniae</td>
</tr>
<tr>
<td>5 (10)</td>
<td>38/F/Thyroid adenoma</td>
<td>Fever, chills</td>
<td>CMZ/45 mg/42 d</td>
<td>700.0</td>
<td>Pneumonia</td>
<td>Septic shock, thyroid storm, DIC, MODS</td>
<td>Recovery</td>
<td>E. aerogenes</td>
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<tr>
<td>6 (11)</td>
<td>28/F/TMG</td>
<td>Fever, sore throat</td>
<td>CMZ/45 mg/NM</td>
<td>2500.0</td>
<td>Acute pharyngitis</td>
<td>Thyroid storm</td>
<td>Recovery</td>
<td>E. coli and K. pneumoniae group G</td>
<td>Nil</td>
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<tr>
<td>7 (12)</td>
<td>18/F</td>
<td>Fever, diarrhoea, abdominal pain</td>
<td>MMZ/40 mg/30 d</td>
<td>5000.0</td>
<td>Typhlitis</td>
<td>NM</td>
<td>Recovery</td>
<td>Streptococcus and K. pneumoniae</td>
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<td>8 (13)</td>
<td>34/F</td>
<td>Fever, chills, sore throat</td>
<td>MMZ/NM/60 d</td>
<td>6000.0</td>
<td>Acute tonsillitis</td>
<td>Septic shock, pneumonia</td>
<td>Recovery</td>
<td>No growth</td>
<td>Throat pus/P. aeruginosa</td>
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<tr>
<td>9 (14)</td>
<td>35/F</td>
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<td>MMZ/30 mg/23 d</td>
<td>4550.0</td>
<td>Acute pharyngitis</td>
<td>NM</td>
<td>Recovery</td>
<td>No growth</td>
<td>Throat pus/group C Streptococcus</td>
</tr>
</tbody>
</table>

CMZ, carbimazole; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; GAD, Graves’ disease; MMZ, methimazole; MODS, multiple-organ dysfunction syndrome; NM, not mentioned; PTU, propylthioracil; TMG, toxic multinodular goitre; WBC, white blood cell count.
dysfunction syndrome (1). All patients but one survived. The fatal case (case 3) was a 48-year-old female, who received methimazole for 49 days before agranulocytosis was detected. She suffered from fever, chills and bloody diarrhoea on admission. Blood cultures grew *P. aeruginosa* and *K. pneumoniae*. The ANC was 11 × 10⁹/l and returned to normal 10 days after discontinuation of methimazole. A colon resection was done because of persistent bloody diarrhoea and the surgical findings showed retroperitoneal abscess, haematoma and rectal perforation. The patient died of persistent, massive, intractable bleeding.

**Discussion**

To our knowledge, this is the first report systematically to review infectious complications and their microbiology related to antithyroid drug-induced agranulocytosis. We found that the incidence of life-threatening infection related to antithyroid-drug-induced agranulocytosis was 0.23%. *P. aeruginosa* was the most common pathogen isolated in these infections. Leukopenia in patients with hyperthyroidism may be caused by thryotoxicosis itself or related to antithyroid drugs. In patients taking anti-thyroid drugs, the absolute neutrophil count rarely falls below 2000 × 10⁹/l, which is not associated with increased risk of infection and does not necessitate drug withdrawal. However, in 0.2%–0.5% of patients treated with antithyroid drugs, agranulocytosis may develop and may be associated with a high risk of life-threatening infections. In our study, the incidence of antithyroid-drug-induced agranulocytosis (0.23%) was comparable to that of previous reports.

Agranulocytosis may occur in any age group, without gender difference, and usually occurs within 2 months of initiation of antithyroid drug therapy, with the elderly being most vulnerable. All but one of our patients developed agranulocytosis within a median of 61 days while taking appropriate therapeutic dosages of thionamides. Recent studies have shown that the mechanism of antithyroid drug-induced agranulocytosis is an immunological phenomenon, rather than a direct toxic effect of antithyroid drugs. Lower dosages of antithyroid drug do not decrease the incidence of agranulocytosis, and it may develop in the second course of therapy even if the first course was uneventful.

The clinical evidence of infectious complications associated with antithyroid-drug-induced agranulocytosis is usually symptomatology in the oropharyngeal region. Patients typically present with fever and sore throat. Similar to other reports, most of our patients suffered from infections in the oral cavity, and the most common clinical diagnoses were acute pharyngitis or tonsillitis. Symptoms may mimic viral infections, and potentially life-threatening pyogenic infections are not usually diagnosed initially. Therefore, timely and appropriate therapy may not be administered. In three of our patients, severe pyogenic infectious complications developed, such as peritonsillar and retropharyngeal abscesses, and airway obstruction or pneumonia, with resultant acute respiratory distress syndrome.

The microbiology of infectious complications of antithyroid drug-induced agranulocytosis is rarely described in the literature. In our study and review of previous reports, we found that the majority of causative micro-organisms were Gram-negative bacilli. In our study and others combined, *P. aeruginosa* was the most common isolate (7/23), followed by *K. pneumoniae* (5/23), *E. coli* (3/23) and *S. aureus* (3/23) in cultures obtained from all infection sites.

*P. aeruginosa* was the leading cause of community-acquired sepsis in patients with antithyroid drug-induced agranulocytosis. The organism causes bacteremia or other invasive infections primarily in a nosocomial setting or in immunocompromised patients, with neutropenia as one of the most important predisposing conditions. Infection with *P. aeruginosa* usually begins with colonization, followed by a break in host defenses with local invasion, and culminates in dissemination and systemic disease, which is associated with high mortality.

In our patients, all episodes of sepsis were community-acquired; patients had no previous chemotherapy or antibiotic treatment. The reason for the development of sepsis might be agranulocytosis and mucosal ulceration. In previous studies, there appears to be a clear relationship between *Pseudomonas* colonization of the respiratory tract and bacterial adherence to buccal epithelial cells. Most of the patients with antithyroid drug-induced agranulocytosis in this review suffered pharyngitis and tonsillitis. With the predominant presentation of pharyngitis and ulceration of the oral mucosa, the oropharynx might have provided a largely unopposed initial break in host defenses to tissue invasion during the period of neutropenia.

Because the occurrence of antithyroid-drug-induced agranulocytosis is sudden and explosive, it is potentially fatal. It is reasonable to obtain a baseline leucocyte count before initiation of antithyroid drug therapy. When therapy is begun, the patient should be instructed to notify the physician immediately if fever or sore throat develops and the leucocyte count must be checked. Discontinuation of the offending antithyroid drugs should be considered when the leucocyte count falls below 1500 × 10⁹/l. Empirical therapy with...
antipseudomonal antibiotics should be administered immediately. Thyroid storm may occur after discontinuation of antithyroid medication and should be properly managed. The circulating granulocyte count usually recovers within 2 weeks after discontinuation of antithyroid drug. Although several clinical studies show that recombinant human G-CSF or GM-CSF (granulocyte-macrophage colony stimulating factor) may hasten the recovery of agranulocytosis, the role of G-CSF in the management of antithyroid drug-induced neutropenia remains uncertain.

In conclusion, our observation and review suggest that patients with antithyroid drug-induced agranulocytosis who present with severe infections should be treated empirically with broad-spectrum antibiotics with antipseudomonal activity.

References


