



Antithyroid Drug-Induced Agranulocytosis: State of the Art on Diagnosis and Management

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Abstract Agranulocytosis is a rare but serious complication of antithyroid drug therapy, and an up-to-date understanding of this topic is important. Both direct toxicity and immune-mediated responses have been described as possible mechanisms. Some major susceptibility loci have recently been identified, which may lead the diagnosis of agranulocytosis into a genomic era. Onset is acute and patients present with symptoms and signs of infection together with high fever. Clinical suspicion is pivotal and should prompt blood sampling. An absolute neutrophil count of $<500/\mu\text{l}$ in the presence of antithyroid drugs establishes the diagnosis. The causative drug should immediately be stopped to prevent further damage. Treatment includes broad-spectrum antibiotics and granulocyte-colony stimulation factor in selected patients. Later, patients will need definitive treatment for hyperthyroidism, usually with radioactive iodine or surgery. The best way to avoid the mortality associated with antithyroid drug-induced agranulocytosis is patient education.

Key Points

Agranulocytosis occurs in 0.2–0.5% of patients with Graves' disease receiving antithyroid drugs.

Both direct toxicity and immune-mediated responses seem to be the cause of agranulocytosis in these patients. Some susceptibility loci have been found to be associated with higher risk.

High fever and sore throat are the most common presenting signs, but patients may also be asymptomatic.

Treatment requires immediate suspension of the antithyroid drug and initiation of broad-spectrum antibiotics. Hematopoietic growth factors may be used. Definitive treatment of hyperthyroidism is required.

Patient education is key to preventing the high morbidity and perhaps mortality of antithyroid drug-induced agranulocytosis.

1 Introduction

Antithyroid drug (ATD) therapy is one option for the treatment of hyperthyroidism, together with surgery and radioactive iodine. Long-term remission of hyperthyroidism can be achieved in about 50% of patients with Graves' disease treated with ATDs [1]. Options include propylthiouracil, carbimazole and its active metabolite methimazole. In clinical practice, propylthiouracil is being

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replaced by carbimazole and methimazole because their biological half-lives are longer (1–2 h vs. approximately 3–5 h for methimazole and carbimazole, with no differences between them [2, 3]) and the risk of severe side effects (hepatotoxicity and agranulocytosis) is lower. The first case of ATD-induced agranulocytosis was described in 1952 by Bartels and Sjogren [4] in their series of 250 cases of treated patients. The patient was receiving methimazole and had previously had agranulocytosis secondary to propylthiouracil treatment. The first death associated with ATD therapy also dates from 1952 [5], when a patient receiving methimazole developed high fever and dyspnea and eventually died of bilateral pneumonia.

ATD-induced agranulocytosis is rare, but the severity of this possibly life-threatening condition means its management is essential to a good prognosis. We summarize the current evidence regarding the definition, epidemiology, risk factors, pathophysiology, clinical presentation, and management of this clinical entity.

2 Methods

We searched PubMed for articles published from January 1952 to September 2016 using the terms ‘agranulocytosis’ and ‘antithyroid drug’ in combination with the terms ‘management,’ ‘treatment,’ and ‘therapy.’ Further relevant published articles were identified through searches of the authors’ personal files, in Google Scholar, and the Springer Online Archives Collection. Articles resulting from these searches and relevant references cited in those articles were reviewed.

3 Definition

Neutropenia can be categorized as mild (absolute neutrophil count [ANC] 1000–1500/ μ l), moderate (ANC 500–1000/ μ l), or severe (ANC < 500/ μ l) [6]. One important definition to bear in mind is that severe neutropenia is not the same as agranulocytosis: the first only refers to the absolute number of neutrophils, whereas the latter includes not only neutrophils but also eosinophils, basophils, and mast cells. Nevertheless, drug-induced agranulocytosis has been defined as ANC < 500/ μ l of blood [7]. In fact, most patients experience ANC < 100/ μ l.

It is important to find a sustained causal relationship between agranulocytosis and ATD. Bénichou and Solal-Celigny [8] previously reported that the following three criteria may be used: (1) onset of agranulocytosis during treatment or within 7 days of previous exposure to the same drug and complete recovery with ANC > 1500/ μ l within 1 month of discontinuation of the drug; (2) recurrence of

agranulocytosis upon re-exposure to an offending drug (rarely seen, because of the high risk of mortality); and (3) criteria of exclusion: any history of congenital neutropenia or immune neutropenia; recent infectious disease (particularly recent viral infection); recent chemotherapy, radiotherapy, or immunotherapy; and an underlying hematological disease. Another important concept is that an ANC < 1000/ μ l may be normal, as in benign ethnic neutropenia [9]. Ethnic groups such as Sephardic and Falasha Jews, Black Bedouin Arabs and some people of African origin may present with such values and still be considered within the normal range.

4 Epidemiology

Agranulocytosis is estimated to occur in 0.2–0.5% of patients with Graves’ disease receiving ATDs [10]. A Dutch study by Van der Klauw et al. [11] reported a relative risk of agranulocytosis of 115 (95% confidence interval [CI] 90.5–218.6) for patients receiving ATDs, which was the highest risk among all evaluated pharmacological agents. Despite the higher risk usually associated with propylthiouracil, Tajiri et al. [12], who studied 15,398 Japanese patients with Graves’ disease, found no difference in incidence of agranulocytosis between patients receiving propylthiouracil and those receiving methimazole. In the largest published series of ATD-induced agranulocytosis, which included 754 cases [10], the mean age of onset was 43.4 ± 15.2 years, nearly 45% of patients were aged in their 40s and 50s and females were more affected than males (6.3: 1 ratio). When compared with untreated patients with Graves’ disease, those with agranulocytosis were older ($p < 0.001$) and more likely to be female ($p < 0.0001$). A more recent review that included 114 patients with ATD-induced agranulocytosis diagnosed in a single Chinese center revealed a higher female-to-male ratio (10.4:1) and similar age of onset (41.7 ± 12.3 years) [13].

5 Pathophysiology

In general, two mechanisms can explain why ATD-induced agranulocytosis develops (Fig. 1) [14]. Some drugs have the potential to be oxidized to reactive metabolites by neutrophils, thus inducing an immune response by activating inflammasomes, thus destroying neutrophils-direct toxicity. Accumulation of ATDs in neutrophils has been demonstrated, favoring this hypothesis [15]. These reactions are mediated by myeloperoxidase, which appears early in granulocyte development during hematopoiesis. The oxidative process can also be accomplished by

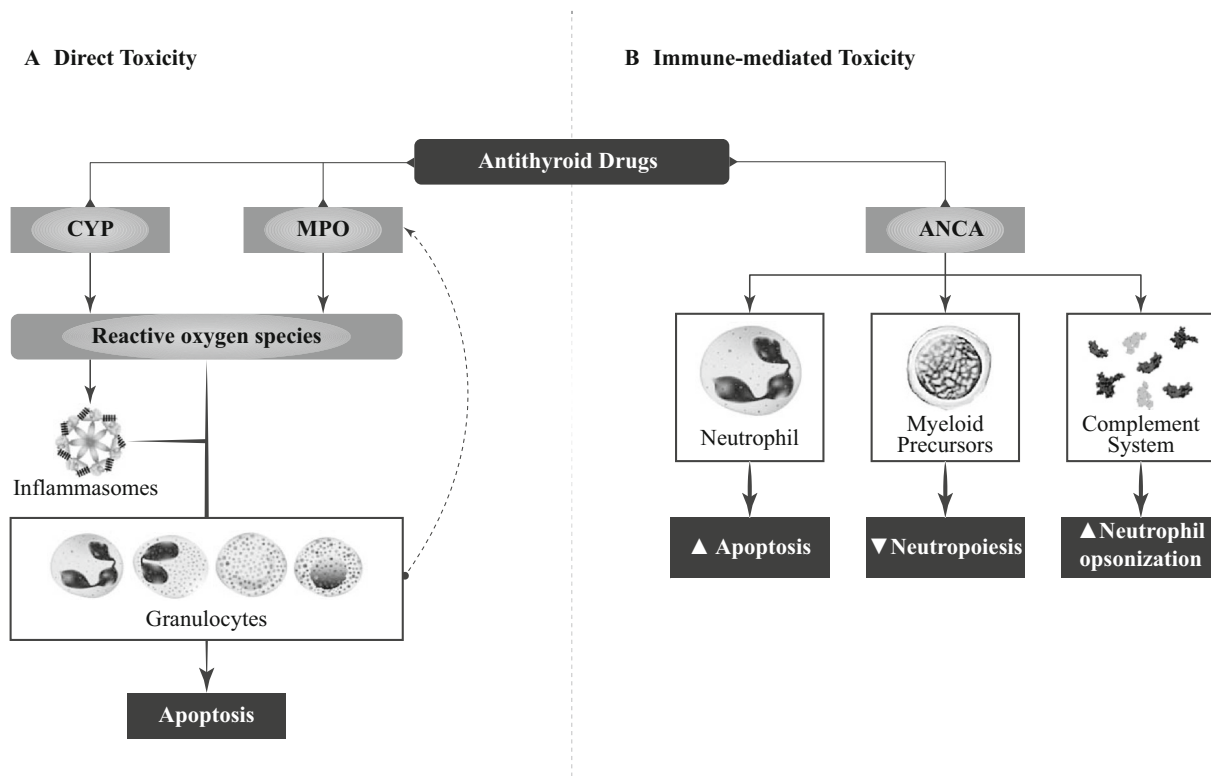


Fig. 1 Mechanisms behind the onset of antithyroid drug-induced agranulocytosis. **a** Direct toxicity: the oxidative process of the antithyroid drug is mediated by myeloperoxidase and cytochrome P450, generating reactive metabolites that will induce apoptosis either directly or via inflammasomes. **b** Immune-mediated toxicity: anti-neutrophil cytoplasmic antibodies may react against neutrophil

antigens as proteinase 3, myeloperoxidase, and cathepsin G after neutrophils are primed and antigens migrate to the cell membrane. Anti-neutrophil cytoplasmic antibodies can also induce opsonization of neutrophils mediated by the complement system and react with myeloid precursors. ANCA anti-neutrophil cytoplasmic antibodies, CYP cytochrome P450, MPO myeloperoxidase

cytochrome P450 (CYP); in fact, this may be the clue to why some drugs that cause neutropenia or agranulocytosis can also cause liver toxicity. Immune mechanisms also seem to have a role in pathogenesis, as previously documented with positive lymphocyte transformation tests [16]. Circulating antibodies against differentiated granulocytes may be responsible for propylthiouracil-induced agranulocytosis, rendering this process immune mediated [17]. These antibodies, which can be anti-neutrophil cytoplasmic antibodies (ANCA), react against specific granules inside the neutrophils when they migrate to the cell membrane, inducing apoptosis. These antibodies can also react with myeloid progenitor cells [17] and induce opsonization of neutrophils, mediated by the complement system [16].

After identifying a genetic background in other drug-induced side effects, Chen et al. [18] demonstrated that human leukocyte antigen (HLA)-B*38:02 and HLA-DRB1*08:03, both by direct HLA genotyping and genome-wide association studies, were independent major susceptibility loci (odds ratio [OR] 21.48; 95% CI 11.13–41.48 for HLA-B*3802 carriers; OR 6.13; 95% CI 3.28–11.46 for HLA-DRB1*08:03; and OR 48.41; 95% CI 21.66–108.22 for those with both alleles). Furthermore, Cheung et al. [19]

found that HLA-B*380201 was strongly associated with carbimazole/methimazole agranulocytosis (OR 265.5; 95% CI 27.9–2528.0) but not with propylthiouracil. These alleles seem to be more prevalent in Asian than in European populations [20], which raises the possibility of structurally similar alleles being responsible for susceptibility in non-Asian populations. Hallberg et al. [21] addressed this question in a Caucasian population, demonstrating an association between ATD-induced agranulocytosis and HLA-B*27:05 and other single nucleotide polymorphisms on chromosome 6.

6 Clinical Presentation

Agranulocytosis usually develops in the first 3 months after ATD therapy is initiated [10], but cases after 5 days up to more than 10 years of exposure have also been described [22]. This difference in time of onset may be related to the disease mechanism, with the immune-mediated process leading to a more rapid destruction of neutrophils as opposed to direct toxicity. The mean duration of treatment with propylthiouracil, carbimazole and methimazole

needed to cause agranulocytosis was found to be 36, 41, and 42 days, respectively [23]. Agranulocytosis can manifest not only after the first treatment with ATD but also in later courses. It can manifest up to eight courses later (with either the same or a different ATD) but usually occurs 5 months after finishing the previous treatment [24].

Symptoms of ATD-induced agranulocytosis do not differ from those of other causes of agranulocytosis. High fever and sore throat are the most frequent signs. Acute pharyngitis and other infections in the oral cavity are the most common clinical diagnoses at presentation [25]. Clinical symptoms of other infections (e.g., severe pneumonia, anorectal or skin infections) may also develop. Sepsis should be suspected, particularly if fever, chills and prostration present suddenly. Despite the typical presentation of fever, 15% of patients can be asymptomatic [16], although they can become symptomatic shortly after diagnosis [12].

Patients with ATD-induced agranulocytosis usually show other signs and symptoms that differ from other causes of agranulocytosis but are related to the thyrotoxic state (tachycardia, tremor, anxiety and pulsatile goiter).

7 Diagnosis and Treatment

Diagnosis is established by an ANC $< 500/\mu\text{l}$ in the context of the clinical picture presented above. Bone marrow examination may be performed to exclude malignancy, to determine cellularity and to assess myeloid maturation. Features include selective reduction or absence of granulocytic precursors with normal or increased erythropoiesis and megakaryocyte proliferation or left-shifted granulopoiesis with few or no mature granulocytes beyond myelocytes [26].

Treatment starts with the identification and immediate discontinuation of the causative agent to prevent further damage (Fig. 2). 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 administer intravenous therapy. Preventive measures are recommended, including good hygiene in high-risk areas such as

the mouth, skin and perineum. The mean time between onset of acute agranulocytosis and normalization of ANC with propylthiouracil, carbimazole, and methimazole are 10, 8, and 10 days, respectively [23].

Hematopoietic growth factors such as granulocyte-colony stimulation factors (G-CSFs) may be used in ATD-induced agranulocytosis and expert opinion from a hematologist should be sought. The use of G-CSF has been shown to reduce the time to hematological recovery, duration of antibiotic therapy and hospitalization and global costs [27, 28]. However, these results should be considered with caution as Fukata et al. [29] conducted a prospective randomized study on the use of G-CSF and found no improvement in recovery time in moderate and severe agranulocytosis. A recent retrospective study replicated these results [13]. A possible explanation for this failure might be an inappropriate dose of G-CSF [30]. In fact, their effectiveness is lower when ANC reduction is severe [31] and the bone marrow shows an absence of granulocytic precursors [26].

The reason for initial prescription of the ATD should not be forgotten. In fact, during recovery from agranulocytosis, the patient will continue to have hyperthyroidism. Alternative ways to treat the hyperthyroid state should be prescribed, because a cross-reaction between carbimazole and propylthiouracil was observed in 15.2% of patients [32]. Therefore, surgery or radioactive iodine seem to be effective options to restore an euthyroid state. In fact, radioactive iodine was demonstrated as a successful option, with 88.8% of patients experiencing euthyroidism after treatment [13].

8 Prevention

The onset of ATD-induced agranulocytosis may be abrupt, with one patient in the case series by Nakamura et al. [10] having a normal ANC in the previous day. This fact stands against the need for periodic routine measurements, as this might not be cost effective. However, as Tajiri et al. [12] reported, this is the best method to diagnose asymptomatic patients. A standardized approach with granulocyte count examination at each visit was shown to correctly diagnose 64 and 94% of patients with agranulocytosis or

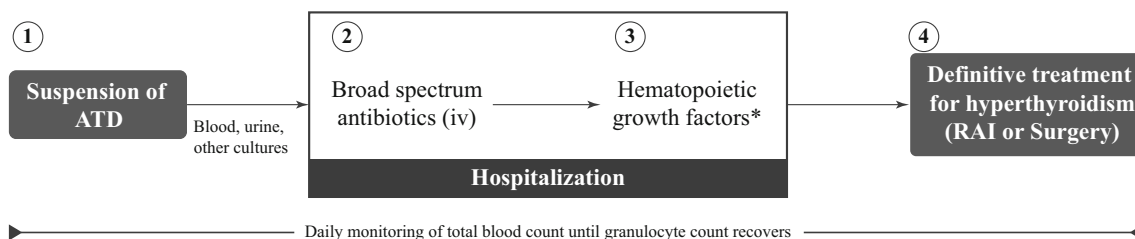


Fig. 2 Flowchart of the treatment of antithyroid drug-induced agranulocytosis. ATD antithyroid drug, *iv* intravenous, RAI radioactive iodine

granulocytopenia, respectively, with no or minimum infection symptoms [33]. On balance, one should try to avoid the most severe and yet unpredictable outcome and thus continue with routine measurements. However, this is still under debate.

The best preventive measure remains patient education at time of prescription and there is still a great margin for improvement in this area. Robinson et al. [34] reported that 60.9% of patients were not aware of the common symptoms of agranulocytosis and 30% of the patients who recalled having received some education on the topic classified this information as “poor”. As delay in diagnosis can increase the risk of mortality, it is essential that the patient seeks medical help soon after the onset of initial symptoms.

9 Conclusion

From the physician’s viewpoint, this serious side effect should be considered in every patient prescribed with any ATD who presents with high fever and other signs of infection. From the patient’s perspective, medical help should be sought immediately after initial symptoms, because a blood cell count with an ANC < 500/ μ l is diagnostic and should prompt the correct approach described above. This is why patient education at time of prescription must not be underestimated and structured programs should be implemented. Recent knowledge about the genetic background of this entity may be important in the future, enabling the identification of the risk alleles in populations with a high prevalence, a tighter granulocyte count measuring in selected patients and the choice of the most appropriate treatment option.

Compliance with Ethical Standards

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Conflict of interest Nuno Vicente, Luís Cardoso, Luísa Barros, and Francisco Carrilho have no conflicts of interest.

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