

Propylthiouracil-induced antineutrophil cytoplasmic antibody-associated vasculitis and agranulocytosis in a patient with Graves' disease

Maria Tomkins, Roxana Maria Tudor, Diarmuid Smith and Amar Agha

Department of Endocrinology and Diabetes, Beaumont Hospital Dublin, Dublin, Ireland

Correspondence
should be addressed
to M Tomkins
Email
mariatomkins200@gmail.com

Summary

This case is the first to describe a patient who experienced concomitant agranulocytosis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis as an adverse effect of propylthiouracil treatment for Graves' disease. A 42-year-old female with Graves' disease presented to the emergency department (ED) with a 2-week history of fevers, night sweats, transient lower limb rash, arthralgia, myalgia and fatigue. She had been taking propylthiouracil for 18 months prior to presentation. On admission, agranulocytosis was evident with a neutrophil count of $0.36 \times 10^9/L$ and immediately propylthiouracil was stopped. There was no evidence of active infection and the patient was treated with broad-spectrum antibiotics and one dose of granulocyte colony-stimulation factor, resulting in a satisfactory response. On further investigation, ANCAs were positive with dual positivity for proteinase 3 and myeloperoxidase. There was no evidence of end-organ damage secondary to vasculitis, and the patient's constitutional symptoms resolved completely on discontinuation of the drug precluding the need for immunosuppressive therapy.

Learning points:

- Continued vigilance and patient education regarding the risk of antithyroid drug-induced agranulocytosis is vital throughout the course of treatment.
- ANCA-associated vasculitis is a rare adverse effect of antithyroid drug use.
- Timely discontinuation of the offending drug is vital in reducing end-organ damage and the need for immunosuppressive therapy in drug-induced ANCA-associated vasculitis.
- Similarities in the pathogenesis of agranulocytosis and drug-induced ANCA-associated vasculitis may offer insight into an improved understanding of vasculitis and agranulocytosis.

Background

This case report describes a patient who experienced concomitant agranulocytosis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis as an adverse effect of propylthiouracil treatment for Graves' disease. Agranulocytosis involves neutrophil destruction due to direct toxicity and immune-mediated induction of ANCA antibodies, and usually occurs within the

first 3 months of therapy, although a delayed onset has been described (1). Patients who experience this side effect require definitive thyroid treatment in the form of radioactive iodine or surgery (1). ANCA-associated vasculitis is a small vessel vasculitis which has varying presentation depending on the degree and nature of organ involvement (2). Propylthiouracil is the most reported drug

implicated in the induction of ANCA-associated vasculitis; however, exact pathogenesis of both ANCA induction and progression to vasculitis in patients taking propylthiouracil remains to be understood (2). This case report is important as, first, it describes a late-onset of agranulocytosis secondary to antithyroid drug use signifying the need for continued vigilance and patient education throughout the course of treatment. Second, it describes ANCA-associated vasculitis, which is a rare, adverse effect of antithyroid drug use. Similarities in the pathogenesis of both these adverse effects may explain why this patient experienced them concomitantly and offers insight into an improved understanding of vasculitis and agranulocytosis.

Case presentation

A 42-year-old female with Graves' disease presented to the emergency department (ED) with a 2-week history of fevers, night sweats, transient lower limb rash, arthralgia, myalgia and fatigue.

Five years previously, she presented with Graves' disease, TSH <0.02 mIU/L, FT4: 39.8 pmol/L (9–16 pmol/L) and TSH receptor antibody positive with a titre of 11.3 IU/L. Thyroid peroxidase antibody was also positive 906 µ/MI (Table 1). Thyroid uptake scan at this time confirmed Graves' disease with homogenous isotope activity (Fig. 1). She had no features of thyroid eye disease or extra-thyroidal manifestations. Initially, she was treated with carbimazole which she self-discontinued once her symptoms had resolved. She was subsequently lost to follow-up due to non-attendance.

Three years later, she presented to the emergency department with thyrotoxicosis and was restarted on carbimazole 30 mg but developed an urticarial rash, lower limb swelling and eosinophilia within 48 h, which resolved on stopping the carbimazole. Following this episode, she was commenced on a propylthiouracil (PTU) titration regime and was referred for thyroidectomy work-up. At the time of presentation to the ED, she had been taking PTU 50 mg daily for 12 months with stable thyroid disease.

Table 1 Biochemistry diagnosing Graves' disease.

Parameter	Level	Normal range
TSH, mIU/L	<0.02	0.27–4.2
FT4, pmol/L	39.8	12–22
TRAB, IU/L	11.3	0.0–1.5
TPO-R Ab	951 U/mL	0–24 IU/mL

FT4, free thyroxine; TPO-R Ab, thyroid peroxidase receptor antibody; TRAB, TSH-receptor antibody; TSH, thyroid-stimulating hormone.

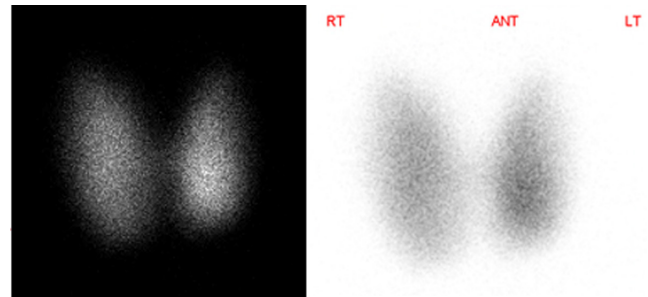


Figure 1 Thyroid uptake scan at diagnosis showing homogenous uptake of radiotracer.

Regarding her family history, one sister had hypothyroidism and there was also a family history of breast cancer on her maternal side. There was no family history of vasculitis or other autoimmune disease.

On examination, she had a low-grade pyrexia of 37.6°C, mild diffusely enlarged non-tender goitre with no evidence of retrosternal extension or thyroid eye disease. She had no signs of active vasculitis with no mouth ulcers, synovitis, rash or sensory deficit. She had mild lower limb oedema.

Investigation

Initial investigations showed a neutrophil count of $0.36 \times 10^9/L$ and white cell count of $1.57 \times 10^9/L$, and the haemoglobin and platelet counts were normal. Blood film analysis demonstrated severe neutropaenia. Biochemistry was normal with normal renal and liver function. Thyroid function was normal with TSH: 1.08 mIU/L and FT4: 15 pmol/L (Table 2). Blood and urine cultures were repeatedly negative. Extended viral screen was also negative. Chest radiograph was normal. Urinalysis showed a small amount of blood with no proteinuria, crystals or casts. Albumin creatinine ratio was normal.

Serum was positive for antinuclear cytoplasmic antibodies (ANCA) with dual positivity for myeloperoxidase (MPO), 6.4 IU/mL (normal range: 0–3.4), and proteinase-3 (PR3), 42 IU/mL (normal range: 0–2). Antinuclear factor was positive. Rheumatoid factor and complement were normal. Antibodies to DNA, RNP, Smith, Ro and La were all negative.

CT thorax abdomen and pelvis showed simple hepatic cysts. There were no concerning features of malignancy.

Treatment

PTU was stopped due to the neutropaenia, and she was treated with broad-spectrum antibiotics. Her neutrophil



Table 2 Initial investigations.

Parameter	Level	Normal range
TSH, mIU/L	1.08	0.38–5.33
FT4, pmol/L	15	7–16
White cell count, $\times 10^9/L$	1.57	4–11
Neutrophils, $\times 10^9/L$	0.36	2–7.5
Lymphocytes, $\times 10^9/L$	1.04	1–4
Eosinophils, $\times 10^9/L$	0.00	0.04–0.40
Basophils, $\times 10^9/L$	0.02	0.01–0.10
Haemoglobin, g/dL	12	11.5–16.5
Platelets, $\times 10^9/L$	179	140–400
Blood film	Severe neutropaenia	
CRP, mg/L	7.8	<5
Urea, mmol/L	4.7	2.5–7.8
Creatinine, $\mu\text{mol/L}$	65	49–90

FT4, free thyroxine; TSH, thyroid-stimulating hormone; CRP, C-reactive protein.

count was initially slow to recover and reached a nadir of $0.19 \times 10^9/L$. She received granulocyte colony-stimulating factor on day 3 of admission to which she responded well (Fig. 2).

Outcome and follow-up

The final diagnosis was that of PTU-induced agranulocytosis occurring late in the course of therapy without evidence of complicating infection. Interestingly, the patient also had ANCA-associated small-vessel vasculitis with constitutional symptoms, myalgia, fever and arthralgia; however, no evidence of renal or respiratory compromise. Both agranulocytosis and ANCA-associated vasculitis resolved with discontinuation of PTU, and immunosuppressive therapy was not required.

Optimal management of Graves' disease was discussed with both the patient and the surgical team, as medical therapy was no longer viable. Following discussion, the patient opted for radioactive iodine (RAI), performed

21 days following admission. She required two doses of radioactive iodine, 584 MBq followed by 772 MBq 3 months later, which yielded an appropriate response. She was not treated with steroids during her radioactive iodine therapy and was treated for hyperthyroidism symptomatically with propranolol 40 mg twice daily. FT4 reduced to 3.4 pmol/L, and she was commenced on levothyroxine 100 μg daily.

At follow-up, 105 days after admission, PR3 titre had reduced from 42 IU/mL to 27 IU/mL and MPO titre remained elevated at 7.2 IU/mL. Her constitutional symptoms resolved completely and there has been no recurrence of the skin rash.

Discussion

This case describes two adverse effects of propylthiouracil (PTU), agranulocytosis and ANCA-associated vasculitis (AAV).

Agranulocytosis refers to a reduction in the absolute neutrophil count to less than 500 cells/ μL which renders the patient susceptible to infection (1). It is a potentially life-threatening complication of several medications and is observed in 0.2–0.5% of patients with Graves' disease prescribed to antithyroid drugs (ATDs) (1). There are two hypotheses to explain the pathogenesis of ATD-related agranulocytosis, direct toxicity and immune-mediated responses. Direct toxicity occurs when drug metabolites are oxidised by neutrophils, creating inflammasomes and reactive oxygen species, resulting in neutrophil apoptosis. These reactions are mediated by myeloperoxidase and cytochrome P450. Immune-mediated neutrophil destruction occurs due to ATD induction of antibodies, commonly ANCA, causing neutrophil apoptosis, complement-mediated neutrophil opsonization and reduced neutropoiesis (1).

Agranulocytosis usually occurs within the first 3 months of ATD treatment, when physicians and patients need to be most vigilant; however, delayed onset agranulocytosis has also been described (1). Research is ongoing into the genetic factors which predispose patients to agranulocytosis. Increased risk of agranulocytosis has been observed with human leukocyte antigens (HLA)-B*38:02 and HLA-DRB1*08:03 in Asian populations and with HLA-B*27:05 in European populations (1).

Clinical presentation of agranulocytosis is often with a sore throat and fever, and diagnosis is made by measuring the absolute neutrophil count ($<500/\mu\text{L}$) (1). Treatment is with prompt discontinuation of the offending drug, broad-spectrum antibiotics (following appropriate blood

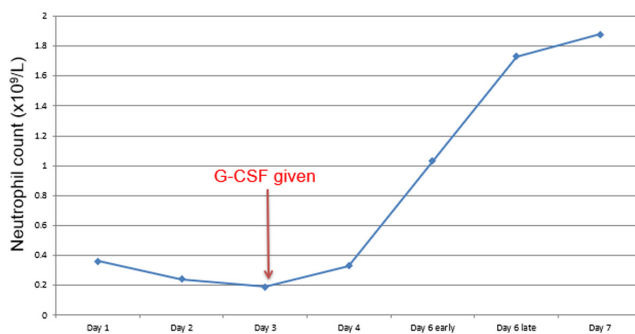


Figure 2 Neutrophil recovery during admission.



and urine cultures) and in some cases haematopoietic growth factors (such as granulocyte colony-stimulation factor) (1). Ultimately the patient will require definitive treatment of Graves' disease with either radioactive iodine therapy or surgery as PTU and carbimazole show cross-reactivity of 15.2% (3).

PTU is the most commonly reported medication causing drug-induced AAV, most commonly MPO-ANCA; however, it has also been associated with carbimazole, minocycline, sulfasalazine, anti-TNF α agents and hydralazine (2). First, the exact mechanism of drug induction of ANCA is not clearly understood but may involve conversion of PTU and its metabolites into cytotoxic products by myeloperoxidase resulting in a T cell, and in turn B cell immunogenic response (2). Second, PTU metabolites may accumulate in neutrophils and modify MPO creating an autoimmune response, and third, drug-induced neutrophil apoptosis, as seen with PTU and sulfasalazine, can induce production of ANCA (2).

On analysing the serum of patients with Graves' disease, Sera *et al.* found MPO-ANCA positivity in 37.5% of patients taking PTU. In contrast, untreated patients and those treated with methimazole did not show ANCA positivity (4). A similar study by Zhao *et al.* found MPO-ANCA positivity in 22.6% of patients treated with PTU. Reassuringly, within this group, clinically evident vasculitis was present in only 28.6% (5). Risk factors for development of PTU-induced AAV were postulated to be the presence of MPO-ANCA, higher titre and affinity of anti-MPO antibodies and the presence of anti-endothelial cell antibodies (5). However, in the largest case review of antithyroid drug-induced MPO-ANCA-associated vasculitis, by Noh *et al.*, there was no significant correlation between severity of vasculitis and MPO-ANCA titre (6).

Noh *et al.* described the variability in clinical presentation of antithyroid drug-induced AAV. In this review, almost 75% of patients were taking PTU with a female preponderance and median onset age of 46 years (6). Renal involvement of vasculitis was most common, followed by respiratory organs and skin. Median time of onset for PTU-induced AAV was 39 months, with a range of 1 to 132 months of therapy (6). Patient characteristics from this study are reflected in the case described, a female 42-year-old patient, taking PTU long term; however, the observance of PTU-induced AAV in this population may purely reflect the prevalence of hyperthyroidism in young females (5).

Primary AAV usually recognizes only one antigen, however, in contrast, PTU-induced AAV commonly

recognises multiple antigens, and patients may show dual positivity for MPO and PR3, as seen in the case described (7). PTU-induced AAV displays a milder course compared to primary AAV, provided PTU is stopped (8). In one observational analysis of long-term outcomes in 15 affected patients, immunosuppressive therapy was only required when there was vital organ involvement, and all patients remained relapse-free even when immunosuppression was discontinued. This suggests that maintenance immunosuppressive therapy may not be required in PTU-induced AAV (9).

One could argue that the patient described in this case did not show clinical signs on presentation of vasculitis, with normal urinalysis and no signs of skin or respiratory organ involvement. However, the patient had constitutional symptoms associated with vasculitis, such as arthralgia, myalgia, night sweats and fatigue. It is unfortunate that the lower limb rash had resolved upon presentation as a skin biopsy which may have provided histopathological evidence of vasculitis. In the setting of vasculitis, constitutional symptoms arise due to release of chemical mediators from inflamed blood vessels and early in disease onset they may be the only presenting symptoms (10). Organ involvement ensues when there is inflammatory cell infiltration causing thinning of the vascular wall, increased vascular permeability and haemorrhage or through occlusion of the vessel due to vascular intimal proliferation and thrombus formation leading to ischaemia or infarction (10). Zhao *et al.* observed MPO-ANCA positivity and constitutional symptoms in some of their reported cases, which resolved rapidly upon cessation of PTU; however, in two cases PTU was continued and organ involvement ensued in the form of end-stage renal failure (5). Therefore, in the case described, presence of agranulocytosis prompted discontinuation of PTU which allowed for rapid resolution of vasculitis-related constitutional symptoms and precluded further progression of AAV.

This case is the first described, showing concomitant agranulocytosis and ANCA-associated vasculitis in a patient taking PTU. The similarities in pathogenesis of these two complications, with involvement of MPO and ANCA, may explain why this patient experienced both adverse events.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.



Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent

The authors declare that written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement

M T is the primary author and contributed to conception, preparation and editing of report. R T contributed to reviewing the report. D S and A A are the senior supervising authors and contributed to manuscript conception and editing. All authors reviewed and approved the manuscript.

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Received in final form 4 December 2019

Accepted 11 December 2019