Thionamides in Thyrotoxicosis with Neutropenia: Culprit or Cure

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Case History

A 59 year old man was admitted with four weeks history of excesive sweating, tremors and generalised weakness. Blood tests showed FT4>100 pmol/L (11.0-25.0), FT3>50 pmol/L (3.1-6.8), TSH<0.01 mU/L (0.27-4.20), TPO antibodies 7.4 U/ml (<34) and neutrophil count of 0.6 $x10^9$/L (1.7-7.5). Past medical history included recurrent episodes of Graves hyperthyroidism, type 2 diabetes and neutropenia of unknown cause under follow-up with haematology. Over the years, he had three spells of hyperthyroism treated with carbimazole: November 2009 - March 2011, August 2011 - March 2012, July 2012 - November 2013. Two days prior to current admission the GP had initiated Carbimazole 20 mg bd. The neutrophil count four months prior to admission was 1.0 $x10^9$/L but his thyroid status was unclear at that stage. An analysis of his previous blood tests showed the neutrophil count trended lower during hyperthyroid spells and improved once euthyroidism was restored (figure 1).

Management

Treatment with carbimazole 20 mg bd was continued under close observation with daily full blood count monitoring. Intravenous steroids and oral propranolol were added to treatment. Over subsequent days, the neutrophil count rose gradually to 2.9 $x10^9$/L (on day 7), FT3 dropped to 16.9 pmol/L and patient felt symptomatically better. He was discharged after a week with outpatient referral for radioiodine ablation of thyroid.

Discussion

Thionamides are known to cause reversible neutropenia in 0.2-0.5% of patients, usually during the first three months, although it can occur anytime during treatment. The mechanism is immune mediated destruction of circulating neutrophils by drug dependent or drug induced antibodies. Of the two thionamides on the European market, carbimazole is less likely to cause agranulocytosis compared to PTU and lower daily doses are safer than higher doses. A baseline neutrophil count of <0.5 $x10^9$/L is a contraindication to initiating thionamide therapy.[1]

Thyrotoxicosis itself lowers the neutrophil count in about 10-15% of patients and the severity of hyperthroidism is an independant predictor of neutropenia.[2] This is thought to be multifactorial, involving disturbances in the maturation and differentiation of the pluripotent cells, direct thyroid hormone toxicity on neutrophils and their precursors and possibly immune mechanisms. Neutrophil count tends to improve as thyrotoxicosis subsides either spontaneusly or under treatment with thionamides. In a recent prospective study[3] nearly half of all euthyroid neutropenic patients attending a haematology outpatients clinic were found to have high titres of anti-TPO antibodies. This study also demonstrated a correlation between high anti-TPO antibodies titres and high anti-neutrophil antibodies.

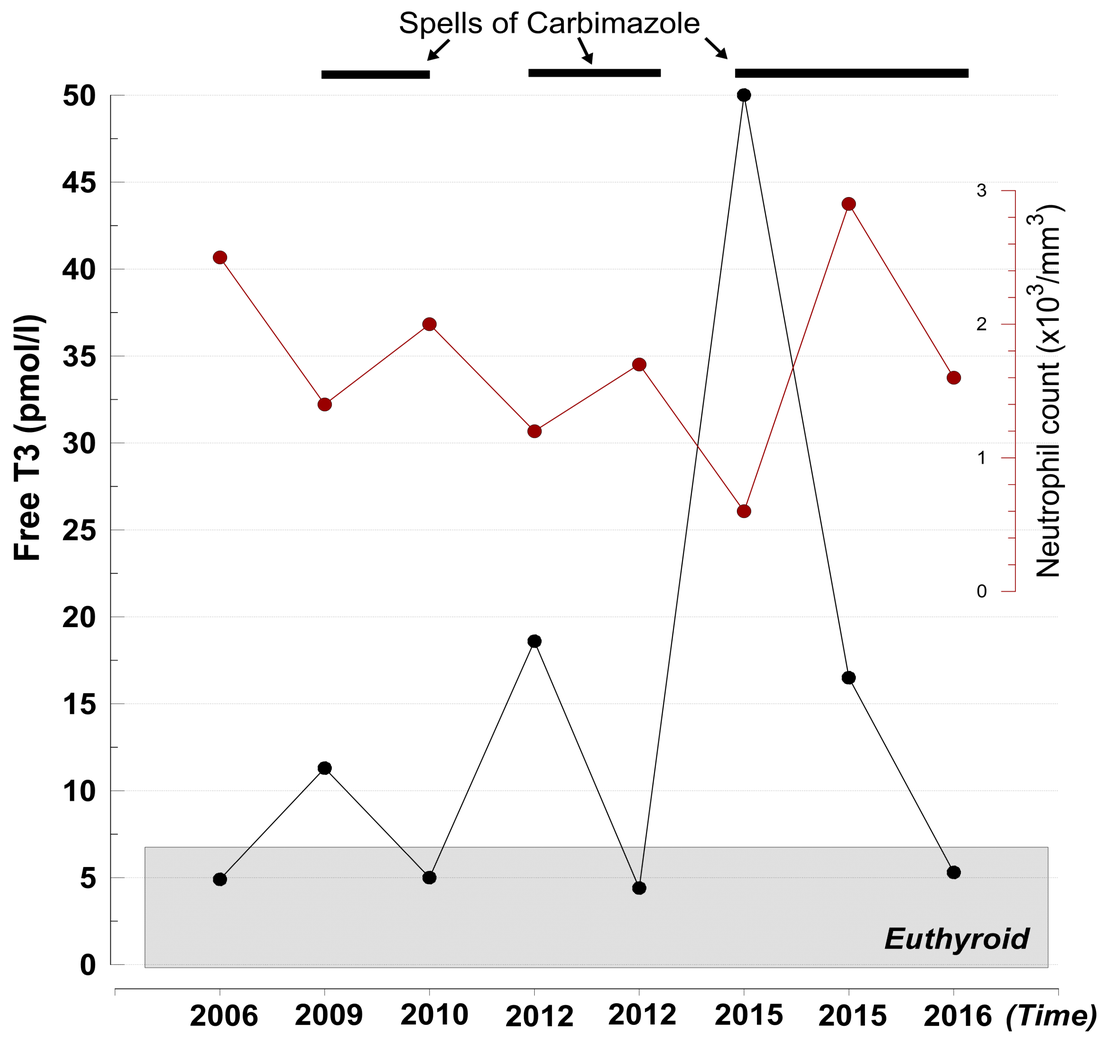

Figure 1: Relationship between neutrophil count and thyroid status (FT3).

Conclusions

Our patient had severe neutropenia related to thyrotoxic state itself. Treatment with carbimazole under close monitoring, resulted in a gradual recovery of the neutrophil count, in parallel with an improvement in the toxic state.

Thyrotoxicosis as well as antithyroid drugs can both cause neutropenia. It is therefore essential to check neutrophil levels at the point of commencement of antithyroid drug treatment as otherwise neutropenia may incorrectly be attributed to antithyroid drugs. In patients who have a neutrophil count >0.5 $x10^9$/ L at baseline, antithyroid drugs could be started under close observation with a plan for alternative treatment if neutropenia worsens.

BES2016 87--EP

Thyroid

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DOI: 10.3252/pso.eu.BES2016.2016

Poster presented at: SfE BES 2016 7-9 November BRIGHTON

PosterSessionOnline.com