Tremelimumab-induced Graves' thyrotoxicosis

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Background

Tremelimumab and Ipilimumab are monoclonal antibodies directed against the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), which acts as an important immune check-point to prevent breakdown of self-tolerance. These anti-CTLA4 antibody-based therapies are effective in treating metastatic melanoma, and potentially other tumours. However, immune-related adverse events including hypophysitis and transient thyroiditis have frequently been reported, usually early on during the therapy. We reported a case of Tremelimumab-induced Graves' thyrotoxicosis after 8 years of immunomodulatory therapy.

Clinical case

- A 55-year old man who developed relapse of metastatic melanoma was enrolled into a phase II trial of Tremelimumab, as second line treatment following progression of disease with conventional chemotherapy.
- He completed 8 cycles of 3-monthly Tremelimumab in 2 years and in view of the excellent disease response, continued to receive the treatment every 6 months on a rollover clinical trial protocol. Thyroid function was monitored 6 monthly.
- Following 8 years of Tremelimumab therapy, he reported 4kg weight loss over a period of 6 months, despite having a good appetite. He had no past history of thyroid or other autoimmune diseases. There was no family history of systemic or organ-specific autoimmune conditions.
- On examination, he looked well, with warm hands and no tremor. He was in sinus rhythm with a pulse of 90 beats per minute. A goitre was not palpable. There was no clinical evidence of Graves' orbitopathy.
- Biochemical tests showed raised serum free T3 (13.0 pmol/L), free T4 (27.6 pmol/L) concentrations and suppressed TSH (figure 1), with elevated thyrotropin receptor antibody (TRab) (5.0 IU/L; reference range 1.0-1.8), in keeping with Graves' thyrotoxicosis.
- He was commenced on carbimazole 40 mg daily. Levothyroxine at a dose of 125mcg daily was added when free thyroid hormones normalised.
- Tremelimumab treatment was initially suspended but recommenced when he was rendered biochemically euthyroid, 8 weeks following antithyroid drug treatment.
- The block and replace therapy for Graves' disease (GD) was withdrawn after 12 months.
- The patient continues to receive 6 monthly Tremelimumab treatment to date and has remained biochemically and clinically euthyroid.

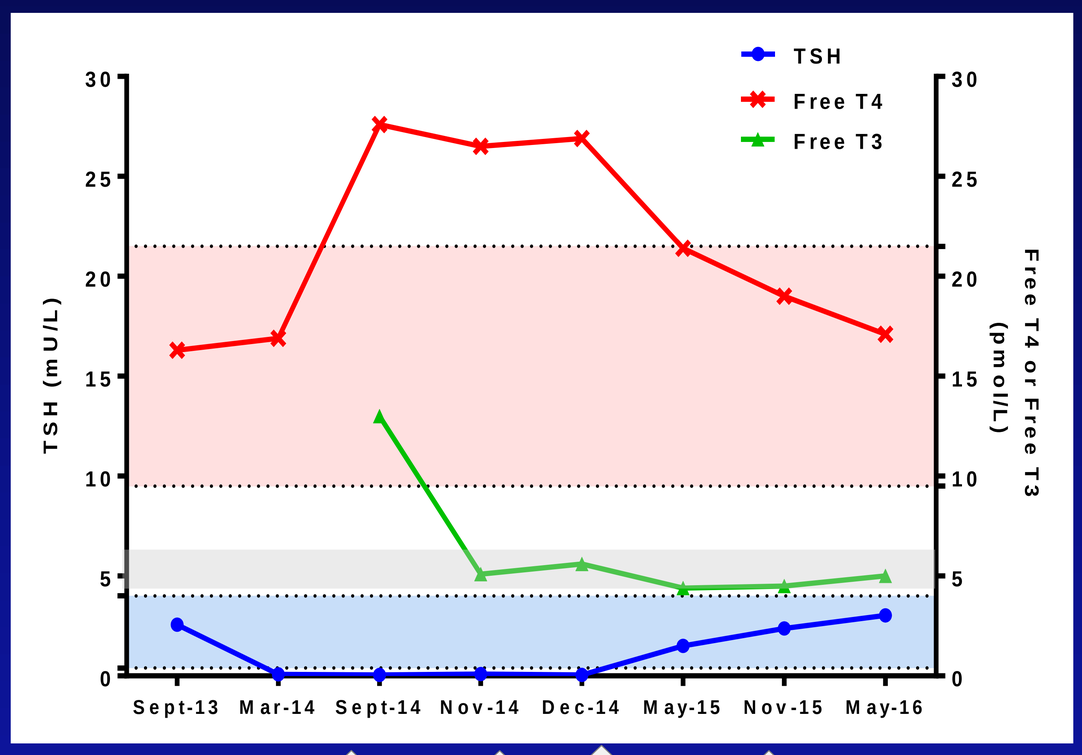

Figure 1. The time-course of free T4, free T3 and TSH profile from 12 months prior to the diagnosis of GD to last review in the clinic.

Shaded horizontal area represent the normal range

- Blue shaded area: TSH (0.3-4.7 mU/L)
- Pink shaded area: free T4 (9.5-21.5 pmol/L)
- Grey shaded area: free T3 (3.5-6.5 pmol/L)

Patient remained biochemically and clinically euthyroid since the discontinuation of antithyroid therapy 12 months ago.

* free T3 level was not checked prior to the diagnosis of GD

Discussion

- Anti-CTLA4 therapy is an immunomodulatory therapy with the potential effect of disrupting systemic immune regulation, which may lead to breakdown of self-tolerance and induction of autoimmune diseases.
- Ipilimumab has been shown to induce hypothyroidism/thyroiditis, euthyroid Graves' orbitopathy and Graves' thyrotoxicosis but all reports have occurred within a relatively short period following treatment. The only reported case of Graves' thyrotoxicosis occurred after 2-4 cycles or 6-12 weeks of Ipilimumab infusion[1].
- To our knowledge, ours is the first reported case of Graves' disease induced by prolonged course of Tremelimumab therapy in a patient with no family or personal history of autoimmune disease, who has subsequently responded well to conventional antithyroid treatment.
- Endocrinologists and oncologists should expect to see more iatrogenic autoimmune endocrine diseases with the increased use of immunomodulatory drugs as cancer therapies.
- The mechanistic profile of anti-CTLA4 induced thyroid dysfunction and the long-term endocrine safety of this therapeutic approach remains unclear. It is important to monitor endocrine function in patients receiving anti-CTLA4 therapies as their effects on endocrine systems could be more latent or prolonged than data from clinical trials suggest.

Reference: 1. Azmat U, Liebner D, Joehlin-Price A et al. (2016) Treatment of Ipilimumab induced Graves' disease in a patient with metastatic melanoma. Case Rep Endocrinol 2087525

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