Tremelimumab-Induced Graves Hyperthyroidism

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What Is Known about This Topic?

- Anti-CTLA-4 immunotherapy used in cancer treatment can cause thyroiditis and Graves disease.

What Does This Case Report Add?

- Transient thyroiditis and Graves disease usually take place within the first 12 weeks following anti-CTLA-4 therapy.
- In this case, Graves disease developed after 8 years of tremelimumab therapy for metastatic melanoma.
- Antithyroid drug therapy was safe and effective alongside anti-CTLA-4 therapy without compromising antitumour treatment efficacy.

Keywords

Tremelimumab · Graves disease · Hyperthyroidism

Abstract

Tremelimumab and ipilimumab are monoclonal antibodies directed against the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and have been used as immunotherapies against immune checkpoints that suppress T-cell activation. Anti-CTLA-4 antibody-based therapies have been shown to be effective in treating various cancers including metastatic melanoma. However, a few immune-related adverse events including hypophysitis and thyroid disorder have been reported, mostly developed within the first year of receiving treatment. We report a case of tremelimumab-induced Graves hyperthyroidism in a 55-year-old man who was diagnosed with metastatic melanoma after 8 years of tremelimumab therapy. He had no personal or family history of thyroid or autoimmune diseases.

His biochemical profile was in keeping with Graves disease, with raised serum free thyroid hormones, suppressed thyroid-stimulating hormone concentration, and raised thyrotropin receptor antibody level. He was treated with carbimazole as part of the block and replace therapy, without complications. Tremelimumab therapy was temporarily discontinued and recommenced when he was rendered biochemically euthyroid. There has been no further relapse of Graves hyperthyroidism since the discontinuation of block and replace therapy. The mechanistic profile of anti-CTLA-4-induced thyroid dysfunction and the long-term endocrine safety of this therapeutic approach remain unclear. It is important to monitor thyroid functions in patients receiving anti-CTLA-4 therapies, as their effects on endocrine systems could be more latent or prolonged than the data from current clinical trials suggest. Antithyroid drug therapy was safe and effective alongside anti-CTLA-4 therapy without compromising antitumour treatment efficacy.

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Introduction

Tremelimumab and ipilimumab are monoclonal antibodies directed against the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). CTLA-4 exerts a suppressive effect on the immune response by acting as a negative co-stimulator. It engages non-MHC cell surface receptors on antigen-presenting cells (known as B7s) to give an inhibitory signal to T-lymphocyte activation [1]. It acts as an important immune checkpoint to prevent the breakdown of self-tolerance. However, it also regulates “tumour immunity” in malignancy via the induction of immune tolerance towards tumour-associated antigens [2, 3]. Hence, strategies that could enhance immune responses against tumour are useful for cancer therapy. Anti-CTLA-4 antibody-based therapies are being increasingly used to treat various malignancies, with a licence to treat metastatic melanoma, where they have been shown to increase overall survival and clinical remission in this disease [4, 5]. However, immune-related adverse events, including endocrinopathies, are common with these therapies [6, 7]. Hypophysitis is among the most common dose-dependent endocrine adverse event in anti-CTLA-4 therapies, followed by thyroid disorders.

This report describes a case of Graves hyperthyroidism after 8 years of tremelimumab therapy. We speculate a causal relationship between tremelimumab therapy and the development of Graves disease, and highlight the importance of full diagnostic workup of cases of thyrotoxicosis in patients treated with anticancer drugs.

Clinical Case

We report a case of a 55-year-old man who was diagnosed with metastatic melanoma on the skin overlying the right parotid gland 14 years ago. The primary lesion was surgically excised. However, he developed nodal relapse in 2005, 7 years after the initial diagnosis, for which he underwent radiotherapy. On subsequent development of further nodal disease and lung metastases, he received 8 cycles of chemotherapy: temozolomide and a poly(ADP-ribose) polymerase inhibitor, rucaparib, in a clinical trial setting. He achieved a partial response after 4 cycles, but the disease progressed after 8 cycles of treatment. He was then enrolled into the phase II trial of tremelimumab, an anti-CTLA-4 monoclonal antibody therapy, as second-line metastatic treatment. He completed 8 cycles of 3-monthly tremelimumab in 2 years and then, in view of the excellent disease response, continued with rollover clinical trial protocol to receive the treatment every 6 months on an ongoing basis, with no evidence of further relapse. Thyroid function was monitored 6 monthly.

Following 8 years of tremelimumab therapy, the patient reported weight loss of 4 kg over a period of 6 months, despite having a good appetite. He had no past history of thyroid or other autoimmune diseases. There was also no family history of systemic or organ-specific autoimmune conditions. He has never smoked. On examination, he looked well, with warm hands and no tremor. He was in sinus rhythm with a pulse of 90 beats/min. Examination of the neck was difficult due to previous surgery and radiotherapy-related scarring; however, a large goitre was not palpable. There was no clinical evidence of Graves orbitopathy. Biochemical tests showed a serum thyroid-stimulating hormone (TSH) which was fully suppressed with a raised free T3 of 13.0 pmol/L (reference range 3.5–6.5) and free T4 of 27.6 pmol/L (reference range 9.5–21.5). Thyroid peroxidase antibodies were elevated at >600 kU/L (reference range 0–34), as was the thyrotropin receptor antibody level, measured at 5.0 IU/L (reference range 1.0–1.8; BRAHMS Kryptor TRAK assay), consistent with Graves disease (Fig. 1). The patient was commenced on carbimazole 40 mg daily and, after 8

Fig. 1. The time course of free T4, free T3, and TSH profiles from 12 months prior to the diagnosis of Graves disease to 6 months after the discontinuation of block and replace therapy (last clinic review). Shaded horizontal areas represent the normal range for the following thyroid parameters: TSH (0.3–4.7 mU/L), free T4 (9.5–21.5 pmol/L), free T3 (3.5–6.5 pmol/L).

weeks, when his serum free T4 concentration normalised, levothyroxine at a dose of 125 µg daily was added. 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 was withdrawn after 12 months. He continues to receive 6-monthly tremelimumab treatment to date and has remained biochemically and clinically euthyroid since the discontinuation of antithyroid therapy 12 months ago.

Discussion

Tremelimumab is a fully human anti-CTLA-4 non-complement-fixing monoclonal antibody (IgG₂ isotype), which is being investigated as a treatment in prostate cancer [8], malignant mesothelioma [9], metastatic melanoma [10], and non-small cell lung cancer [11]. CTLA-4 is a type 1 glycoprotein expressed on the surface of T cells and serves as a co-inhibitory molecule in T-cell activation [12]. The mature protein of CTLA-4 is constitutively expressed in the CD4+CD25+ regulatory T (Treg) cells but is only found on the surface of activated T (CD4+ and CD8+) lymphocytes, B cells, monocytes, and dendritic cells [13–15]. It competes with the co-stimulatory molecule CD28 for the B7 ligands (CD80 and CD86) on antigen-presenting cells, leading to a reduction in B7-CD28 co-stimulatory signals and T-cell activation [13]. CTLA-4 induces Treg cell suppression and anergy by blocking the costimulatory signals in antigen-presenting cells and attenuates T-cell response (T-cell response hypo-signalling) via direct negative signalling through its cytoplasmic tail [16]. Although anti-CTLA-4 therapy has been proven to be effective in tumour rejection and in the reduction of tumour-mediated immune tolerance via enhanced T-cell activation, it has the potential effect of disrupting systemic immune regulation, particularly in the breakdown of self-tolerance. A spectrum of immune-related adverse events has been reported among patients receiving anti-CTLA-4 therapy, including colitis, arthritis, hepatitis, cutaneous reactions, uveitis, pancreatitis, and nephritis [6]. From an endocrine perspective, cases of lymphocytic hypophysitis, thyroiditis, and adrenalitis have been reported [6, 7].

A single nucleotide polymorphism CT60A/G (rs3087243) in the 3' untranslated region of human CTLA-4 locus on chromosome 2q33 has been associated with multiple autoimmune diseases, including type 1 diabetes, Graves disease, rheumatoid arthritis, and celiac disease [17–21]. The CTLA-4 and the HLA locus together confer up to 50% of the inherited susceptibility to Graves

disease in UK cohorts [22]. From clinical experience, thyroid dysfunction is commonly reported following anti-CTLA-4 therapy [7]. Ipilimumab has been shown to induce hypothyroidism/thyroiditis [23], euthyroid Graves ophthalmopathy [24], and Graves thyrotoxicosis [25]. In a single centre specialising in immune modulatory therapy, 6% of the 256 patients were found to have hypothyroidism/thyroiditis following ipilimumab therapy, with a male to female ratio of 2:3 [26]. One patient treated with tremelimumab was reported to have developed asymptomatic thyroiditis followed by hypothyroidism, which required long-term thyroxine replacement therapy [27]. The previously reported cases of anti-CTLA-4-induced thyroid dysfunction occurred within a relatively short period following ipilimumab infusion, after 2–4 cycles or 6–12 weeks of treatment.

The data on autoimmunity toxicity remain sparse for tremelimumab as it is only used in clinical trials. Transient thyroiditis is commonly seen within the first year of tremelimumab treatment [28], and it is rather surprising to observe the “latent autoimmune toxicity” as in this case. However, much prolonged onset of autoimmune thyroid dysfunction has been observed with other immunotherapy, such as alemtuzumab, a human anti-CD52 monoclonal antibody therapy, with onset ranging from 6 to 61 months after the first course of treatment [29, 30]. One might suggest that our case was an incidental finding of isolated Graves disease rather than CTLA-4-induced thyroid disease. However, the absence of personal or family history of autoimmune diseases renders strong autoimmune predisposition less likely. The mechanistic profile of anti-CTLA-4-induced thyroid dysfunction and the long-term endocrine safety of this therapeutic approach remain unclear and should be explored further.

It is difficult to predict when and who will develop anti-CTLA-4-induced Graves disease, but endocrine adverse effects may be delayed. Hence, it is important to monitor thyroid function regularly (at least 6 monthly) while patients are on an immunomodulatory agent, preferably with baseline thyroid function and thyroid autoantibodies prior to commencing anti-CTLA-4 therapy. Although the majority of dysthyroid episodes may be due to thyroiditis with a self-limiting clinical course, Graves disease can also occur. A full diagnostic workup by an endocrinologist aiming to characterise the aetiology of thyrotoxicosis is paramount, as management will be dictated by a precise diagnosis.

To conclude, this report illustrates a case of Graves hyperthyroidism following prolonged anti-CTLA-4 therapy, and highlights the importance of thyroid function

monitoring and of making a precise diagnosis of the cause of thyrotoxicosis. Antithyroid drug therapy was safe and effective alongside anti-CTLA4 therapy without compromising anti-tumour treatment efficacy.

Disclosure Statement

We declare that all authors have no competing interests.

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