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Graves' Disease Induced by Immune Checkpoint Inhibitors: A Case Report and Review of the Literature

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Abstract
Introduction: In the last few years, immune checkpoint inhibitors (ICPis) have become a common treatment of cancer. ICPis are associated with peculiar immune side effects, termed immune-related adverse events (irAEs). Thyroid dysfunction is a common irAE, but clinical manifestation, severity, and pathogenesis can be variable. While destructive thyroiditis and hypothyroidism are the most common thyroid irAEs induced by ICPis, autoimmune hyperthyroidism (Graves' disease) is rare. We describe a case of a Graves' disease induced by anti-PD-1 therapy and we review the previous reports on this issue. ***Case Presentation:*** A 51-year-old man developed an overt autoimmune hyperthyroidism 2 months after he had started nivolumab (anti-PD-1) therapy for a metastatic non-small cell lung cancer. Although TSH-receptor autoantibodies (TRAb) were negative, the persistence of hyperthyroidism, the hypervascular pattern at thyroid ultrasound, and the high uptake at thyroid scintigraphy were all features suggestive of Graves' disease. Methimazole was started with the prompt restoration of euthyroidism. TRAb remained undetectable during the entire follow-up. ***Conclusions:*** Autoimmune hyperthyroidism can be induced by anti-PD-1 treatment. TRAb were negative in both cases of nivolumab-induced Graves' disease described to date. A correct differential diagnosis between destructive thyroiditis and autoimmune hyperthyroidism is crucial for the appropriate treatment.

Introduction

Immune checkpoint inhibitors (ICPis) are powerful new drugs for treatment of cancer. These monoclonal antibodies trigger immune system against cancer cells, blocking inhibitory signals of T-cells, specifically cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1). So far, several randomized clinical trials have demonstrated the efficacy of these molecules in improving the progression-free survival in several types of cancer (e.g., melanoma, non-small cell lung cancer, kidney cancer, breast cancer). ICPis can induce side effects, the so-

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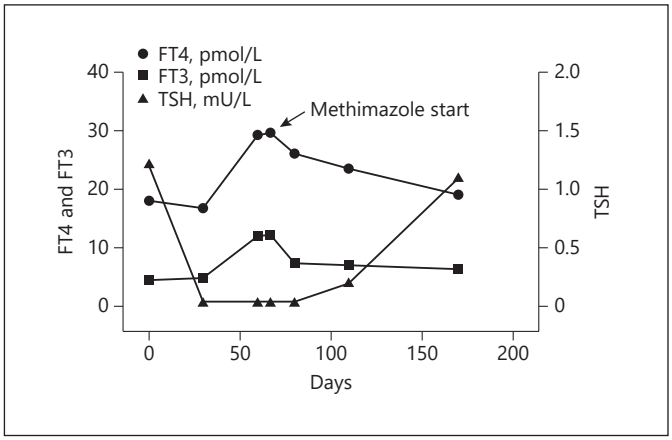

Fig. 1. Time course of thyroid function of the patient during treatment with nivolumab. Time 0: first infusion of anti-PD-1 (Nivolumab).

called immune-related adverse events (irAEs). Among irAEs, endocrinopathies are frequent and include thyroid dysfunction, hypophysitis, insulin-deficient diabetes mellitus, and primary adrenal insufficiency. Thyroid dysfunction is the most common ICPi-induced endocrinopathy, with transient thyrotoxicosis due to destructive thyroiditis and hypothyroidism frequently reported in clinical trials of ICPis. On the contrary, Graves' disease has been described in only eight patients during ICPis treatment, five during anti-CTLA-4 and three during anti-PD-1 treatment. We report the fourth case of Grave's disease induced by anti-PD-1, the second with an overt hyperthyroidism.

Case Presentation

A 51-year-old male was referred to us because he had experienced palpitations, heat intolerance, and insomnia after the fourth infusion of nivolumab (3 mg/kg every 14 days) for a metastatic non-small cell lung cancer. Thyroid function tests before the start of nivolumab treatment showed euthyroidism, with free thyroxine (FT4) 18.1 pmol/L (normal range 9.0–21.8), free triiodothyronine (FT3) 4.5 pmol/L (4.1–8.7), thyroid-stimulating hormone (TSH) 1.22 mU/L (0.4–4.0) (Fig. 1), associated with negative thyroperoxidase autoantibodies (TPOAb), negative thyroglobulin autoantibodies (TgAb), and unremarkable thyroid ultrasound. In the 3 months prior to referral, no administration of iodinated contrast media was reported. At physical examination, we observed increased heart rate and sweaty skin and no signs of Graves' ophthalmopathy. Thyroid function tests were suggestive of overt thyrotoxicosis: FT4 29.3 pmol/L, FT3 11.2 pmol/L, TSH 0.04 mU/L (Fig. 1). TSH-receptor autoantibodies (TRAb) as well as TPOAb and TgAb turned out negative one more time. We re-evaluated the patient 1 week later. Thyroid function tests were comparable (FT4 29.6 pmol/L, FT3 11.4 pmol/L), and at ultrasound, the thyroid was enlarged (20 mL), hypoechoic, and with a mild hypervascularity at Doppler. ^{131}I thyroid scintigram showed an increased and diffuse uptake (3 h uptake 40%; normal range 15–25%).

The patient started methimazole, 20 mg/day. At the following observation, 30 days later, symptoms of thyrotoxicosis had disappeared and thyroid function tests had significantly improved: FT4 25.7 pmol/L, FT3 7.4 pmol/L, TSH 0.2 mU/L (Fig. 1). Within 60 days of treatment with methimazole, euthyroidism was restored: FT4 19 pmol/L, FT3 6.29 pmol/L, TSH 1.1 mU/L. Methimazole was therefore tapered down to 5 mg/day, with maintenance of euthyroidism. Thyroid autoantibodies remained negative throughout the entire follow-up (Fig. 1). The patient died 4 months later because of cancer progression.

Discussion

In clinical trials and subsequent clinical practice, thyroid dysfunction has been reported as a common adverse effect during ICPi treatment [1]. A similar overall incidence of hypothyroidism (7–10%) has been estimated for the three types of drugs. At variance, the incidence of thyrotoxicosis differs according to the ICPi regimen, being lower (3.4%) during the anti-CTLA-4 treatment and higher (13.0%) when anti-CTLA-4 and anti-PD-1 are combined [1]. Among cases of thyrotoxicosis, the large majority are transient forms due to destructive thyroiditis, which are usually followed by persistent hypothyroidism, while Graves' disease (hyperthyroidism and/or Graves' ophthalmopathy) has been rarely reported [1, 2].

Graves' disease is typically characterized by diffuse goiter, hyperthyroidism, and, in 50% of patients, ophthalmopathy [3]. Including the present, a total of nine cases of Graves' disease, five after anti-CTLA-4 and four after anti-PD-1 treatment, have been reported (Table 1). It is worth noting that four patients (two after anti-CTLA-4 and two after anti-PD-1 treatment) developed isolated hyperthyroidism and five (three after anti-CTLA-4 and two after anti-PD-1 treatment) euthyroid Graves' ophthalmopathy (Table 1). At variance with the common presentation of spontaneous Graves' disease, no patient developed both autoimmune hyperthyroidism and Graves' ophthalmopathy. Of note, euthyroid Graves' ophthalmopathy is very uncommon after other immunotherapy drugs (e.g., interferon and alemtuzumab); in these settings, ophthalmopathy is usually associated with hyperthyroidism [4, 5].

The patient we describe herein developed an overt and symptomatic thyrotoxicosis 2 months after nivolumab was started. The characteristics that allow the clinician to differentiate between thyrotoxicosis due to destructive

Table 1. Case reports on Graves' disease induced by ICPis

First author, year	ICPis	Hyper-thyroid-ism	GO	Cycle/ time	FT4 (pmol/L)	FT3 (pmol/L)	TRAb	Iodine/ ^{99}TC uptake	Vascular pattern	Treatment
Anti-CTLA-4										
Borodic [8], 2011	Ipilimumab	No	Yes	II/6 weeks	na	na	Positive	na	na	Glucocorticoids
Min [9], 2011	Ipilimumab	No	Yes	IV/12 weeks	14.1	na	Positive	na	na	Glucocorticoids
McElnea [10], 2014	Ipilimumab	No	Yes	III/6 weeks	23.7	na	Negative	na	na	Glucocorticoids
Azmat [11], 2016	Ipilimumab	Yes	No	II/6 weeks	46.8	15.1	Positive	High	na	Methimazole Thyroidectomy
Gan [12], 2017	Tremelimumab	Yes	No	XX/8 years	35.5	13.0	Positive	na	na	Carbimazole
Anti-PD-1										
Park [13], 2018	Pembrolizumab	No	Yes	III/9 weeks	na	na	na	na	na	Glucocorticoids
Campredon [14], 2018	Nivolumab	No	Yes	III/6 weeks	15.4	4.3	Negative	na	na	Glucocorticoids
Iadarola [15], 2019	Nivolumab	Yes	No	II/4 weeks	17.5	8.7	Negative	High	Normal	Methimazole
Brancatella (present case), 2019	Nivolumab	Yes	No	IV/8 weeks	29.3	11.1	Negative	High	Hyper-vascular	Methimazole

ICPis, immune checkpoint inhibitors; GO, Graves' ophthalmopathy; na, not available.

Table 2. Destructive thyroiditis and Graves' hyperthyroidism during ICPi therapy: differential diagnosis

	Destructive thyroiditis	Graves' hyperthyroidism
Duration	Transient (days to weeks)	Persistent (months to years)
Lag time from ICPi start	Short (weeks)	Variable (weeks to years)
Iodine uptake	Low	High
FT3/FT4 ratio	Low	High
TgAb and TPOAb	+/–	+/–
TRAb	–	+/–
Treatment	No/symptomatic	Anti-thyroid drugs (radioiodine thyroidectomy)

ICPi, immune checkpoint inhibitor.

thyroiditis and autoimmune hyperthyroidism ensuing during ICPi treatment are: severity (mild to moderate vs. moderate to severe), duration (self-limited vs. persistent), lag time (weeks vs. weeks to years), ^{131}I uptake (low vs. high), FT3/FT4 ratio (low vs. high), and vascular pattern at color Doppler (low vs. high) (Table 2).

In our patient, TPOAb, TgAb, and TRAb were undetectable during the entire follow-up. The role of thyroid autoantibodies in the pathogenesis of ICPi-related thyroid dysfunction is debated. While Osorio and colleagues [6] reported an association between positive TPOAb and positive TgAb and thyroid dysfunction induced by ICPi therapy, this association was not observed in other studies.

The pathogenic role of TRAb in Graves' disease is well established and TRAb are positive in up to 95% of spontaneous cases [7]. In the clinical practice, TRAb are a useful tool in the differential diagnosis of thyrotoxicosis. Anti-CTLA-4-induced Graves' disease was reported to be associated with positive TRAb (Table 1). In our patient, as well as in the other cases of nivolumab-induced Graves' disease, TRAb were persistently negative (Table 1). The finding that all the cases of anti-PD-1-induced Graves' disease are associated with negative TRAb is surprising.

Destructive thyroiditis is usually self-limited and symptoms can be managed by beta blockers. In case of severe thyrotoxicosis or in patients with high cardiovascular risk, treatment with glucocorticoids can be required [1]. Conversely, Graves' hyperthyroidism is persistent and requires anti-thyroid treatment. Anti-thyroid drugs showed a good efficacy in restoring and maintaining euthyroidism in all cases of ICPi-induced Graves' hyperthyroidism. Treatment with thyroidectomy or radioiodine remains an option when hyperthyroidism is not manageable with anti-thyroid drugs. One patient underwent total

thyroidectomy for hyperthyroidism during neck dissection for residual melanoma (Table 1). In all cases, Graves' ophthalmopathy was successfully treated with high dose of glucocorticoids (Table 1).

In conclusion, Graves' disease has been reported during ICPis. Both anti-CTLA-4 and anti-PD-1 can induce Graves' hyperthyroidism, although the presentation can be different. A correct differential diagnosis between destructive thyroiditis and Graves' hyperthyroidism is required because treatment of the two conditions is different.

Statement of Ethics

All diagnostic and therapeutic procedures were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from the individual participant included in the report.

Disclosure Statement

The authors have no conflict of interest.

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Author Contributions

Both Alessandro Brancatella and Francesco Latrofa contributed to the final version of the manuscript. All authors discussed the results and conclusions of this work.

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