Thyroid dysfunction in patients undergoing Nivolumab cancer treatment: Case reports and review of literature

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ABSTRACT

Introduction: The recent development of anticancer treatments focused on disrupting the signaling pathways has arrived as a promising alternative for conditions previously untreatable. Nivolumab is a second-generation monoclonal antibody that works as a negative regulatory agonist of the programmed cell death protein 1 (PD-1) receptor expressed by B and T lymphocytes and natural killer cells, preventing the binding of PD-1 to its ligands programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2), therefore protecting healthy tissues. As a result of an increased immune system activity, this may provide inflammatory side effects known as immune-related adverse events (IRAEs). Thyroid dysfunction (TD) is frequently observed in patients using Anti-PD-1.

Case Report: Our case report refers to two patients of 67 and 75 years old, feminine and masculine genders, respectively, that developed Nivolumab-induced TD with transient hyperthyroidism and posterior evolution to hypothyroidism. Both were treated with Levothyroxine after thyrotoxicosis phase.

Conclusion: Thyroid dysfunction has been a recurrent IRAE described in patients using Anti-PD-1 and it is usually a treatable condition. Our patients manifested a less common TD known as lymphocytic thyroiditis. Because there is an increased tendency of using immune checkpoint inhibitors, both cases highlight the importance of close monitoring to detect the development and progression of TD, avoiding preventable morbidity and allowing to maintain cancer therapy.

Keywords: Immune checkpoint inhibitors, Neoplasms, Nivolumab, Thyroiditis

INTRODUCTION

The recent development of anticancer treatments focused on disrupting the signaling pathways has arrived as a promising alternative for conditions previously untreatable [1]. Cancer cells have the capability to stimulate different immune checkpoint pathways that harbor immunosuppressive functions [2]. Therefore, the immune checkpoint inhibitors (ICIs) target regulatory pathways in T cells to enhance antitumor immune responses [3].

The antibody against programmed cell death 1 (Anti-PD-1) receptor called Nivolumab is a second-generation
monoclonal antibody that works as a negative regulatory agonist of the PD-1 receptor expressed by B and T lymphocytes and natural killer (NK) cells, preventing the binding of PD-1 to its ligands programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2). It also protects healthy tissues (Figure 1) [1]. The purpose is to block inhibitory pathways that act as an obstacle to adequate and efficient antitumor T cell responses [4]. Nivolumab was approved by the U.S. Food and Drug Administration (FDA) in 2014 for the treatment of various cancers including melanoma and non-small cell lung cancer (NSCLC) [4, 5].

As a result of an increased immune system activity, the immune checkpoint blockage may provide side effects which are usually called immune-related adverse events (IRAEs). The organs frequently affected by this Anti-PD-1 drug are: gastrointestinal tract, endocrine glands, skin, and liver [5]. Thyroid dysfunction (TD) is frequently observed in patients using Anti-PD-1 (Nivolumab and Pembrolizumab), and here we report two cases of patients who developed Nivolumab-induced TD [6].

![Figure 1: Mechanism of action of immune checkpoint inhibitors Anti-PD-1 and Anti-PD-L1. The surface of immune cells such as B and T lymphocytes and natural killer cells express the receptor programmed cell death ligand 1 (PD-1). PD-1 binds to its ligand (programmed cell death ligand 1–PD-L1) and prevents T cells from exterminating cancer cells. Antitumor immune responses occur when antibodies Anti-PD-1 and/or Anti-PD-L1 connect to its respective receptor at the surface of the lymphocyte T cell, inhibiting the binding of PD-1 to PD-L1.](image)

**CASE SERIES**

**Case 1**

A 67-year-old woman with diagnosis of melanoma at the dorsal region and metastasis to lungs who began Nivolumab treatment and developed moderate cutaneous reaction requiring therapy with prednisone 1 mg/kg/day. The patient had partial recovery of skin adverse event with glucocorticoid. A blood test was performed after initial administration of Nivolumab showing signs of hyperthyroidism: thyroid-stimulating hormone (TSH) of 0.013 mU/L [reference values (RV): 0.3–4.0] and free thyroxine (fT4) of 2.1 ng/dL (RV: 0.9–1.8). Because there were no clinical signs of thyroid hyperfunction, it was decided to observe and repeat the exam further along treatment. After eight months of Nivolumab, the patient developed overt hypothyroidism with TSH of 25.0 mU/L and fT4 of 0.3 ng/dL. Levothyroxine was initiated daily at the dose of 50 mcg, with satisfactory response.

**Case 2**

A 75-year-old man with diagnosis of NSCLC with metastasis to lungs and liver began treatment with Nivolumab and after two months showed alteration of thyroid function compatible with hyperthyroidism (TSH of 0.03 mU/L and fT4 of 2.2 ng/dL). It was decided to maintain clinical observation and repeat exams after three weeks. Results revealed hypothyroidism (TSH of 19.0 mU/L and fT4 of 0.5 ng/dL) with positivity of Anti-thyroidperoxidase antibody (Anti-TPOAb). The TSH receptor antibody (Anti-TSIAb) was negative. Therapy with levothyroxine was started with initial dose of 25 mcg per day and progressively increased until 75 mcg per day, to achieve euthyroidism. The patient evolved to death due to the severity of his clinical condition.

**DISCUSSION**

The case reports showed two patients in use of Nivolumab that developed initially transient hyperthyroidism with posterior evolution to hypothyroidism. Thyroid dysfunction is described in patients using Nivolumab in a range of 0–18.5% [1]. The most common manifestations of Nivolumab TD are hypothyroidism, either overt or subclinical with an incidence of 8%, primary autoimmune hyperthyroidism or Graves’ disease in up to 2.8%; and silent or painless thyroiditis, also known as lymphocytic thyroiditis, with incidence of 1.6% [7]. Thyroid dysfunction caused by ICI is more prevalent in females, being consistent with what is found in the general population [1].

Both hypothyroidism and painless thyroiditis have an autoimmune pathogenesis that involves humoral and cellular response mechanisms which need further research. Hypothyroidism, usually caused by Hashimoto’s disease, consists of a chronic autoimmune inflammation of the thyroid gland [1]. The Graves’ disease may be suggested due to the presence of Anti-TSIAb, which activates TSH receptors and increase thyroid hormone production [1]. Studies speculate that lymphocytic thyroiditis occurs due to the fact that Nivolumab induces the reduction of immune feedback in healthy thyroid tissue, leading to the development of an inflammatory process (thyroiditis) [1]. Frequently, this painless thyroiditis is expressed with an initial transient hyperthyroidism (destruction...
of follicular cells leading to the release of thyroid hormone) followed by hypothyroidism, and some patients return to euthyroidism or develop permanent hypothyroidism [1]. A study with 657 patients using ICI therapies (monotherapy or combinations) described hypothyroidism in 84% of the patients who had documented transient thyroiditis [8].

In order to differentiate primary autoimmune hyperthyroidism from lymphocytic thyroiditis, the gold standard exam is radioactive iodine uptake scintigraphy. A low uptake reveals thyroiditis, whereas an increased uptake of 25% or over indicates Graves’ disease [1]. Unfortunately, our patients were not submitted to this exam during hyperthyroidism evaluation. Moreover, patients with TD due to ICI may express elevated levels of anti-TPOAbs in approximately 50% of the cases, which was observed in one of our cases [8].

Thyroid disorders are frequently asymptomatic and are monitored by routine laboratory tests during follow-up [9]. According to Gonzalez-Rodriguez et al. [1], 67% of patients who develop thyroiditis are asymptomatic during thyrotoxicosis phase and this is what we observed in our patients. Therefore, we may hypothesize that they developed an inflammatory process similar to lymphocytic thyroiditis as a result of Nivolumab therapy, considering that the first exam evidenced hyperthyroidism with rapid transition to hypothyroidism.

Van Kooten et al. [10] described two cases with thyroiditis onset 2–4 weeks after initiating treatment with Nivolumab, an evolution similar to that of our patients. The authors speculate that the underlying pathophysiological mechanism is a transient destructive thyroiditis, a conclusion based on the relatively rapid resolution and temporarily increased FDG uptake observed with F-fluorodeoxy glucose positron emission tomography (FDG-PET/CT). For this reason, thionamides are not recommended to treat the initial hyperthyroidism phase [10]. Orlov et al. [11] and de Filette et al. [12] also described painless thyroiditis with thyrotoxicosis and subsequent hypothyroidism in patients using Anti-PD-1 monoclonal antibody therapy.

The incidence of IRAE with PD-1 or PD-L1 inhibitors is different from that reported with cytotoxic T lymphocyte-associated antigen-4 monoclonal antibodies (Anti-CTLA-4-Ipilimumab) agents [13]. Hypophysitis has been more commonly described in patients using Ipilimumab reaching 5.6% [7]. Ipilimumab induces TD in a range of 0–7.4% of the patients treated. On the other hand, TD was more incidental in patients who used Anti-PD-1 and the most common manifestation was hypothyroidism with Pembrolizumab and Nivolumab reaching 8.5% and 8%, respectively [7]. For both medications, hypothyroidism is the most frequent thyroid dysfunction followed by hyperthyroidism [1]. PD1 is expressed by T and B lymphocytes and NK cells while CTLA4 is expressed only by T lymphocytes. For this reason, when these surface proteins are inhibited, the cells tend to proliferate. This elucidates the reason why Anti-PD1 therapies could lead to more thyroidopathies compared to Anti-CTLA4 [1].

A meta-analysis published in 2018, with 38 clinical trials including 7551 patients, revealed that the incidence of hypothyroidism and hyperthyroidism was higher in individuals using combination therapy. Also, those on PD-1 inhibitor therapy had an increased risk of developing hypothyroidism and the study evidenced that hyperthyroidism was significantly greater with anti-PD-1 compared to anti-PD-L1 [14].

Thyroid disorders are more likely to be observed in patients receiving Anti-PD-1 therapy who have positivity for antithyroid antibodies [5]. This occurs due to the additive effect of the T-cell-mediated immunity and the way that the Anti-PD-1 therapy modulates humoral immunity, intensifying preexisting thyroid autoimmunity [5]. In a study with Nivolumab, 26% of the patients who developed TD presented antithyroid antibodies at baseline, whereas 36% presented them along the treatment, which reinforces the immune-mediated determinant of this condition [1]. Interestingly, the histologic evaluation of Hashimoto’s thyroiditis (autoimmune thyroiditis) shows evidence of infiltration by lymphocytic B cells and cytotoxic T cells. PD-1 is expressed by T and B lymphocytes and, for this reason, when these surface receptors are inhibited the cells tend to multiply, inducing immune response which exacerbates due to preexisting thyroid autoimmunity [1].

According to Kimbara et al. [15], in a study with 168 patients, the incidence of TD was significantly higher in those with thyroid autoimmunity compared to individuals without. Particularly in this analysis, the presence of antithyroglobulin antibodies (TgAb) before Nivolumab was associated with a large and significant hazard ratio of TD compared to that of TPOAb. In addition to that, 74% of 23 patients who developed TD presented increased levels of TgAb during Nivolumab treatment and 2 patients with TPOAb alone at baseline became positive for TgAb when developed TD. None of our patients had a previous history of TD and unfortunately, they had no previous dosage of antibodies against the thyroid.

There are strong recommendations in most papers that screening of thyroid function and its autoantibodies should be performed at baseline and every 4–6 weeks as Nivolumab is administered intravenously every 2 weeks, or if the patient presents any symptoms suggestive of TD [3, 16].

In a study with 657 patients undergoing therapy with ICI, in which 56 presented TD (14 were receiving Nivolumab), the median time to thyrotoxicosis was 6 weeks after starting the ICI therapy and the median time to hypothyroidism was 17 weeks [8]. In our case report the time to hypothyroidism after starting Nivolumab was 32 weeks in case 1 and 11 weeks in case 2.

If thyroiditis is speculated, it might be prudent to observe the transient hyperthyroidism and once established hypothyroidism initiate Levothyroxine. During thyrotoxicosis period therapy with beta blocker may be considered and although in some references
steroids are not routinely recommended during this phase, in severe symptomatic hyperthyroidism we may consider suspending ICI and initiating corticosteroids [8–10]. Depending on the clinical condition of the patient, it might be necessary to evaluate cortisol levels aside from thyroid function, to exclude the possibility of adrenal insufficiency before initiating Levothyroxine [9].

It is uncommon for patients to discontinue Nivolumab treatment because of TD, as it can be controlled with thyroid drugs during the cancer treatment [3]. The discontinuation rate of Anti-PD-1/PD-L1 ranges from 3 to 8% due to IRAE, whereas for Ipilimumab it reaches up to 15% [9]. When administered Ipilimumab in combination with Nivolumab, the discontinuation rate increases to 36% [9].

Latest data suggested that the development of IRAEs might be associated with higher response rates to cancer treatment and a longer median duration of response, as seen in a study from 2019 where the response rate was 38.2% among the 34 patients in the thyroiditis group and 17.4% among the 69 patients from non-thyroiditis group (p = 0.028), while the median progression-free survival was 10.1 months in the thyroiditis group and 3.7 months in the non-thyroiditis group [17]. From that point of view, the presence of IRAE (specifically TD) might grant a better prognosis for the patient due to a more effective and potent immune-mediated response to therapy [9]. Yamauchi et al. [6] described a curious relationship between TD consequent to ICI and good prognosis in NSCLC patients, although sample sizes were small (approximately 50 patients in two different studies). The study explains that there is evidence that target antigens exist at the lung and the thyroid gland, so if the patient develops TD as an IRAE, immune responses to lung cancer are expected as antibodies recognize antigens in both sites [6]. Our second patient had NSCLC, but the disease aggravated and he didn’t survive.

CONCLUSION

The use of ICI therapy has increased in the last decade and IRAEs have a high incidence with these medications. Endocrine adverse events, especially TD, are frequent in this scenario. Close monitoring is necessary to detect the development and progression of TD, avoiding preventable morbidity and allowing to maintain cancer therapy. Therefore, endocrinologists and oncologists must work together to make sure that the patient is being followed appropriately.

REFERENCES

1. Gonzalez-Rodríguez E, Rodríguez-Abreu D, Spanish Group for Cancer Immuno-Biotherapy (GETICA). Immune checkpoint inhibitors: Review and management of endocrine adverse events. Oncologist 2016;21(7):804–16.
2. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: Recent progress and potential biomarkers. Exp Mol Med 2018;50(12):1–11.
3. Tanaka R, Fujisawa Y, Maruyama H, et al. Nivolumab-induced thyroid dysfunction. Jpn J Clin Oncol 2016;46(6):575–9.
4. Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348(6230):56–61.
5. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378(2):158–68.
6. Yamauchi I, Yasoda A, Matsumoto S, et al. Incidence, features, and prognosis of immune-related adverse events involving the thyroid gland induced by nivolumab. PLoS One 2019;14(5):e0216954.
7. de Filette J, Andreescu CE, Cools F, Bravenboer B, Velkeniers B. A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. Horm Metab Res 2019;51(3):145–56.
8. Iyer PC, Cabanillas ME, Waguespack SG, et al. Immune-related thyroiditis with immune checkpoint inhibitors. Thyroid 2018;28(10):1243–51.
9. Ferrari SM, Fallahi P, Galetta F, Citi E, Benenga S, Antonelli A. Thyroid disorders induced by checkpoint inhibitors. Rev Endocr Metab Disord 2018;19(4):325–33.
10. van Kooten MJ, van den Berg G, Glaudemans AWJ, et al. Transient thyrotoxicosis during nivolumab treatment. Neth J Med 2017;75(5):204–7.
11. Araujo PB, Coelho MCA, Arruda M, Gadelha MR, Neto LV. Ipilimumab-induced hypophysitis: Review of the literature. J Endocrinol Invest 2018;33(11):1159–66.
12. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and meta-analysis. JAMA Oncol 2018;4(2):173–82.
13. Kimbara S, Fujiwara Y, Iwama S, et al. Association of antithyroglobulin antibodies with the development of thyroid dysfunction induced by nivolumab. Cancer Sci 2018;109(11):1358–90.
14. O’Malley G, Lee HJ, Parekh S, et al. Rapid evolution of thyroid dysfunction in patients treated with Nivolumab. Endocr Pract 2017;23(10):1223–31.
15. Lei M, Michael A, Patel S, Wang D. Evaluation of the impact of thyroiditis development in patients receiving immunotherapy with programmed cell death-1 inhibitors. J Oncol Pharm Pract 2019;25(6):1402–11.
Author Contributions

Bárbara Gehrke – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.

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