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CASE OF INDUCED GRAVE'S DISEASE BY NIVOLUMAB TREATMENT

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ნივოლუმაბით ინდუცირებული გრეივსის დაავადების შემთხვევა

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი

რეზიუმე

იმუნური მაკონტროლებელი მოლეკულების ინჰიბიტორები (იმმი) სიახლეა კიბოს მკურნალობაში. მიუხედავად იმუნოთერაპიის წარმატებული შედეგებისა ონკოლოგიაში, გარდამავალი თირეოტოქსიკოზი და ჰიპოთირეოზი წარმოადგენს ფარისებრი ჯირკვლის დისფუნქციით მიმდინარე, იმუნური გვერდითი მოვლენების ყველაზე ხშირ ენდოკრინულ გამოვლინებას. თუმცა, ლიტერატურა ასევე აღწერს იმმი-ით გამოწვეული გრეივსის დაავადების რამდენიმე შემთხვევას. ჩვენ წარმოგიდგენთ, გრეივსის დაავადებას, რომელიც განვითარდა ანტი-PD-1 თერაპიის შედეგად. მეტასტაზური მელანომის მქონე, 63 წლის მამაკაცს ნივოლუმაბის მეექვსე ინფუზიის შემდეგ განუვითარდა - ტაქიკარდია, პალპიტაცია, გადაჭარბებული ოფლიანობა და ნეგატიური სიზმრები. მისი ფარისებრი ჯირკვლის ფუნქციური ტესტი (ფჯფ) იყო დარღვეული და მას მკურნალობა ჩაუტარდა მეთიმაზოლით და პროპრანოლოლით. მეთიმაზოლის დაწყებიდან ათი კვირის შემდეგ, ფჯფ-ი დაუბრუნდა ნორმას და სიმპტომებიც ალაგდა. მიუხედავად იმისა, რომ გრეივსის დაავადება წარმოადგენს იმუნოთერაპიის იშვიათ გართულებას, სასიცოცხლოდ მნიშვნელოვანია მისი განვითარების გათვალისწინება, რათა მოხდეს დაავადების სწრაფი დიაგნოსტირება და მკურნალობა, რაც უზრუნველყოფს ონკოპაციენტებში სიცოცხლის მაღალ ხარისხს და გადარჩენას.

Introduction. More than twelve decades ago, William Coley made the initial connection between immunology and oncology to find effective cancer-targeting techniques [1]. At the end of the 20th century, James Allison discovered the immune checkpoints, which led to the development of novel immunotherapy against tumors and awarded him with the Nobel Prize. Immune checkpoint inhibitors (ICIs) are powerful new drugs for the treatment of cancer. These monoclonal antibodies trigger the immune system against cancer cells, blocking inhibitory signals of T-cells, namely cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Programmed death 1(PD-1), and Programmed death ligand 1 (PD-L1) [2]. Immune checkpoint inhibitors markedly increased cancer patients' progression-free survival, but they also brought on a wide range of adverse events that are referred to as immune-related adverse events (irAEs). While immunotherapy affects nearly every organ, the skin, gastrointestinal, and endocrine systems are particularly affected. Among immune-related endocrinopathies, thyroid dysfunction is the most common. The majority of immune-related thyroid dysfunctions are caused by transient thyrotoxicosis and hypothyroidism [3], only several cases of ICI-induced Grave's disease are described in the literature. We report a case of Grave's disease acquired after anti-PD-1 therapy.

Case Presentation. A 63-year-old male was sent to our endocrinological department with complaints of tachycardia, palpitations, excessive perspiration, and vivid horrific dreams after the sixth infusion of anti-PD-1 monoclonal antibody - Nivolumab (240mg IVq 2 weeks) for metastatic melanoma. He had nightmares even after the third injection, but he ignored them until now. A thyroid ultrasound and thyroid function tests (TFTs) were performed before the beginning of Nivolumab treatment. TFTs were normal, and thyroid ultrasonography revealed no alterations. He and his family have no previous history of thyroid illness. On physical examination, he showed tachycardia at 122 beats per minute, occasional irregular rhythm, T/A at 145/95mmHg, dewy skin, and no symptoms of ocular problems. ECOG was 2.

Thyroid function tests were indicative of Grave's disease: TSH- < 0.008 μIU/ml (NR: 0.4-4.2), FT4- 38.96pmol/L (NR: 12-22), FT3- 13.11 pmol/L (NR: 3.1-6.8), thyrotropin receptor antibodies (TRAb)

- 14,2 IU/L (NR< 1.0), TPO antibodies and Tg antibodies were negative. The ultrasound was also suggestive of Grave's disease, with the thyroid gland enlarged to 23mL, hyperechoic, and hypervascularity in the parenchyma on Doppler imaging. ^{99m}Tc-pertechnetate scintigraphy was not done because of the patient's unwillingness. Thus, we recognized his thyrotoxicosis as a new-onset Graves' disease after Nivolumab therapy based on TFTs and ultrasound and initiated treatment with methimazole 25mg/day and propranolol.

At the next follow-up, 2 weeks later, the symptoms of thyrotoxicosis subsided, but the TFT was still abnormal. The patient came for a check-up every fortnight. 10 weeks after the initiation of methimazole, TFTs were normalized, and all the symptoms disappeared (Table 1). The patient was relieved to return to sleep without nightmares. Consequently, methimazole was reduced to 5mg/day while keeping euthyroidism stable. The patient has resumed his immunotherapy treatment, and he has completed the 7th dose infusion.

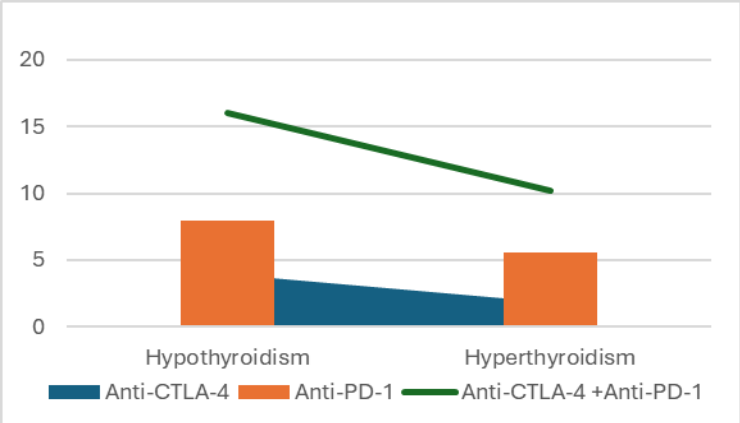
Table 1. Thyroid tests and symptoms examined before methimazole medication, after weeks 6 and 10

TFTs & Symptoms	Week 0	Week 6	Week 10
TSH (NR: 0.4-4.2 µIU/ml)	0.008	0.15	0.96
Free T4 (NR: 12-22 pmol/L)	38.96	24.66	18.53
Free T3 (NR: 3.1-6.8 pmol/L)	13.11	8.34	4.1
TRAb (NR< 1.0 IU/L)	14.2	5.42	0.71
ECOG	2	1	0
Tachycardia/Palpitation	Present	Absent	Absent
Perspiration	Present	Present	Absent
Horrific dreams	Present	Present	Absent

Discussion. Main mechanism of ICI therapy is removing the brakes of immune system, thus facilitating destruction of cancer cells by activated tumor-specific T cells. This can cause adverse effects which affect the whole organism through autoimmunity. Thyroid dysfunction has been noted as a common side effect of ICI medication and can occur during the treatment with any type of ICI (Figure 1) [1,4].

At this time, the exact mechanisms of thyroid irAEs induction by each of the ICIs is not fully understood. Many theories have emerged, and the most accepted current theory involves an interplay between genetic factors, cellular autoimmunity and humoral immunity, supported by T-cells cross-reactivity, increased levels of interferon gamma-inducible chemokines (which attract T-cells), the contribution of ADCC and the HLA-DR allele which is involved in autoimmunity.

Figure 1. The prevalence (%) of immune checkpoint inhibitor-induced hypothyroidism and hyperthyroidism with monotherapy vs combination treatment



Anti-PD-1 antibody treatment induces transient thyrotoxicosis. It seems to be primarily a T-cell mediated process, supported by the presence of $CD8^+$ T-cells in the thyroid, and $CD4^-CD8^-$ T-cells in the thyroid and blood of the patients [5,6]. For example, it is reported that PD-1 is not expressed on T-cells from pembrolizumab-induced thyroiditis, which supports a T-cell mediated mechanism, rather than a B-cell mediated one [7]. Th1/Th2 balance has been reported in favor of Th1, with increased levels of IL-2 (which might stimulate autoreactive lymphocytes), IL-1β, GM-CSF and decrease of Il-8, G-CSF and MCP-1 [8,9]. Thyrotoxicosis is usually followed by persistent hypothyroidism, which is mediated by – Th1 and Th17 cells. Decreased Th2 cell activity during thyrotoxicosis [8,9] can explain less possibility of development of hyperthyroidism – Graves' disease which is mediated by autoantibodies.

Graves' disease is a thyroid autoimmune condition that is triggered by TRAbs. Production of autoantibodies is responsibility of Th2 activity (mainly mediated through L-4). The lymphocytes in Graves' thyroid tissue are responsible for producing these antibodies [10]. TRAbs may exhibit either stimulatory, inhibitory, or neutral effects as antibodies. Stimulating thyroid-stimulating hormone receptor antibodies (also known as TSIg) enhance the production and function of sodium-iodide symporter and G proteins. As a result, there is an elevation in the absorption of iodine, the production of thyroid hormones, and their release, along with an increase in the growth and survival of thyroid cells, which leads to the manifestation of hyperthyroidism symptoms [11,12]. Patients with blocking TRAbs occasionally have clinical manifestation of hypothyroidism caused by inhibiting TSH activity. Neutral antibodies bind to the TSH receptor's hinge region without influencing TSH function. Although they have been linked to thyroid cell stress and apoptosis, their clinical importance remains unclear [13].

The patient we discussed manifested overt hyperthyroidism. In this particular instance, the criteria that enable the doctor to discriminate between autoimmune hyperthyroidism and thyrotoxicosis caused by destructive thyroiditis are the existence of TRAbs and the vascular pattern during color Doppler imaging. The limitations of this case study include the lack of scintigram and the absence of a baseline (pre-immunotherapy) test for TRAb assay. On the other hand, the fact that both the restoration and maintenance of euthyroidism by anti-thyroid drug - methimazole in this individual were successful is indicative of an accurate diagnosis and therapy.

In conclusion, even though Grave's disease is a relatively uncommon consequence of ICI therapy, it is very necessary to always keep it in mind to ensure that cancer patients get prompt diagnosis and treatment to maintain a good quality of life and overall survival.

Ethics Statements. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration. The study protocol was approved by the Tbilisi State Medical University Ethical Committee on Human Research. Informed consent was obtained from a patient included in the study.

Disclosure Statement. The authors have no conflict of interest.

References

1. Yin, Q., Wu, L., Han, L., Zheng, X., Tong, R., Li, L., Bai, L., & Bian, Y. (2023). Immune-related adverse events of immune checkpoint inhibitors: a review. Frontiers in immunology, 14, 1167975. https://doi.org/10.3389/fimmu.2023.1167975
2. Brancatella, A., Viola, N., Brogioni, S., et al. (2019). Graves' Disease Induced by Immune Checkpoint Inhibitors: A Case Report and Review of the Literature. European thyroid journal, 8(4):192–195. https://doi.org/10.1159/000501824
3. Zhan, L., Feng, H. F., Liu, H., et al. (2021, June 10). Immune Checkpoint Inhibitors-Related Thyroid Dysfunction: Epidemiology, Clinical Presentation, Possible Pathogenesis, and Management. Frontiers in Endocrinology. https://doi.org/10.3389/fendo.2021.649863
4. George, A. S., Fernandez, C. J., Eapen, D., & Pappachan, J. M. (2021). Organ-specific Adverse Events of Immune Checkpoint Inhibitor Therapy, with Special Reference to Endocrinopathies. European Endocrinology, 1(1), 21. https://doi.org/10.17925/ee.2021.1.1.21

5. Lima Ferreira J, Costa C, Marques B, Castro S, et al. Improved survival in patients with thyroid function test abnormalities secondary to immune-checkpoint inhibitors. Cancer Immunology Immunotherapy (2021) 70:299–309. doi: 10.1007/s00262-020-02664-y
6. Kotwal A, Gustafson MP, Bornschlegl S, Kottschade L, Delivanis DA, Dietz AB, et al. Immune checkpoint inhibitor-induced thyroiditis is associated with increased intrathyroidal T lymphocyte subpopulations. Thyroid (2020) 30:1440–50. doi: 10.1089/thy.2020.0075
7. Delivanis DA, Gustafson MP, Bornschlegl S, Merten MM, Kottschade L, et al. Pembrolizumab-induced thyroiditis: Comprehensive clinical review and insights into underlying involved mechanisms. J Clin Endocrinol Metab (2017) 102:2770–80. doi: 10.1210/jc.2017-00448
8. Corsello SM, Barnabei A, Marchetti P, de Vecchis L, Salvatori R, Torino F. Endocrine side effects induced by immune checkpoint inhibitors. J Clin Endocrinol Metab (2013) 98:1361–75. doi: 10.1210/jc.2012-4075
9. De Moel EC, Rozeman EA, Kapiteijn EH, Verdegaal EME, Grummels A, et al. Autoantibody development under treatment with immune-checkpoint inhibitors. Cancer Immunol Res (2019) 7:6–11. doi: 10.1158/2326-6066.CIR-18-0245
10. MCLACHLAN, S. M., PEGG, C. A. S., ATHERTON, M. C., et al. (1986, February). TSH RECEPTOR ANTIBODY SYNTHESIS BY THYROID LYMPHOCYTES. Clinical Endocrinology, 24(2), 223–230. https://doi.org/10.1111/j.1365-2265.1986.tb00766.x
11. Saito, T. (1997, October 1). Increased Expression of the Na+/I- Symporter in Cultured Human Thyroid Cells Exposed to Thyrotropin and in Graves' Thyroid Tissue. Journal of Clinical Endocrinology & Metabolism, 82(10), 3331–3336. https://doi.org/10.1210/jc.82.10.3331
12. Vassart, G. (1992, August 1). The thyrotropin receptor and the regulation of thyrocyte function and growth. Endocrine Reviews, 13(3), 596–611. https://doi.org/10.1210/er.13.3.596
13. Morshed, S. A., Ando, T., Latif, R., & Davies, T. F. (2010, November). Neutral Antibodies to the TSH Receptor Are Present in Graves' Disease and Regulate Selective Signaling Cascades. Endocrinology, 151(11), 5537–5549. https://doi.org/10.1210/en.2010-0424

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SUMMARY

Immune checkpoint inhibitors (ICIs) are powerful new drugs for the treatment of cancer. Immune-related adverse events (irAEs), despite their successful use in oncology, resulted in a wide range of adverse effects. Transient thyrotoxicosis and hypothyroidism cause the majority of immune-related thyroid dysfunctions, but there are also reported a few cases of ICI-induced hyperthyroidism. We present a case of Graves' disease resulted from anti-PD-1 therapy. A 63-year-old male developed tachycardia, palpitations, excessive perspiration, and vivid, horrific dreams after the sixth infusion of Nivolumab for metastatic melanoma. His thyroid function test (TFT) was abnormal, and he was treated with methimazole and propranolol. Ten weeks after starting methimazole, the TFT returned to normal, and the symptoms subsided. In a nutshell, even though Grave's disease is a rare complication of immunotherapy, it is very important always keep it in mind to ensure quick access to prompt diagnosis and treatment to maintain a good quality of life and overall survival.

Keywords: Grave's disease, Nivolumab, hyperthyroidism, TRAb