

## Late manifestation of Immunotherapy induced hypothyroidism with high antibody titers

Keerthana Haridas<sup>1\*</sup>; Hajira Amir<sup>2</sup>

<sup>1</sup>Internal Medicine Icahn School of Medicine Mount Sinai St Luke's/West, USA.

<sup>2</sup>Mount Sinai Beth Israel, PGY5, Endocrinology, Icahn School of Medicine Mount Sinai Beth Israel.

**Received Date** : June 08, 2022  
**Accepted Date** : July 05, 2022  
**Published Date** : July 27, 2022  
**Archived** : [www.jcmimagescasereports.org](http://www.jcmimagescasereports.org)  
**Copyright** : © Keerthana Haridas 2022

**\*Corresponding Author:** Keerthana Haridas, PGY2, Internal Medicine Icahn School of Medicine Mount Sinai St Luke's/West 1000, 10th Avenue, NY 10019, USA.  
Tel: 9293893737  
Email: [keerthana.haridas@mountsinai.org](mailto:keerthana.haridas@mountsinai.org)

### Abstract

Immune checkpoint inhibitors are widely used in the treatment of cancers. They are known to cause multisystem immune related adverse effects, including endocrinopathies. Primary thyroid dysfunction has been documented as an adverse effect of immunotherapy. We report a case of primary hypothyroidism detected in a patient after treatment with anti-PD-L1 agent, Atezolizumab. The patient presented with altered mental status 6 months after the initiation of immunotherapy. TSH was measured as part of the workup for encephalopathy, revealing TSH >20 with undetectable free T3, free T4. Anti TPO antibodies were elevated to >7500 IU/ml with anti thyroglobulin antibodies elevated to about 50U/ml. Thyroid ultrasound showed a diffusely heterogeneous gland with no other abnormalities. Patient was detected to have metastatic disease to the brain and spinal cord likely causing her change in mental status and was treated with steroids and radiation after which she improved. She was started on Levothyroxine 50mcg daily and discharged on the same dose. This case illustrates the need for measurement of TSH in all patients prior to the initiation of immunotherapy given the possibility of development of primary thyroid dysfunction mediated by inflammatory thyroiditis in these settings.

### Introduction

Immune checkpoint inhibitors (ICPi) have begun to be widely used in the treatment of cancers in the last two decades. They have been approved in the treatment of melanoma, renal cell carcinomas, lung cancer and other solid tumors [1, 2]. They block checkpoint proteins including Cytotoxic T Lymphocyte Antigen-4(CTLA-4) and Programmed Death-1 (PD-1) present on the surface of immune cells, cells of other organ systems as well as cancer cells in addition to their ligands such as the PD-Ligand 1. These checkpoints help downregulate immune responses and prevent persistent or overactive immune responses against antigens including auto-antigens. However, this also renders cancer cells resistant to immune destruction [1, 2]. Inhibition of these immune checkpoints therefore up-regulates the activation and functioning of different immune pathways, increasing tumor susceptibility to immune surveillance and destruction. In doing so, they decrease self tolerance and cause multisystem autoimmune manifestations/immune related adverse effects. (irAEs) [1, 2]. Autoimmune endocrinopathies are known to occur as an adverse effect of ICPi therapy [1, 2]. Furthermore, In comparison to other irAEs, endocrinopathies are more likely to be irreversible [2]. Primary thyroid dysfunction manifests as clinical and subclinical hypothyroidism and hyperthyroidism, largely caused by

inflammatory thyroiditis. Hypothyroidism is more common than hyperthyroidism which seems more transient and likely to evolve into hypothyroidism. [1, 2, 3]. We report a case of anti-PD-L1 induced hypothyroidism discovered 6 months after the initiation of therapy.

### Case Report

79 y old female with past history of B/L breast cancer (s/p neoadjuvant chemotherapy, lumpectomy and hormonal therapy), stage IV poorly differentiated small-cell carcinoma of left lung (TxN3M1c) with metastases to neck, mediastinum, abdomen and spine treated with steroid therapy, palliative radiotherapy, combination chemotherapy-immunotherapy followed by mono therapy with with Atezolizumab, presented with altered mental status and complaints of generalized body pain and fatigue. She denied focal neurologic deficits. She denied any preceding trauma. No infectious symptoms were endorsed. She endorsed no symptoms of thyroid dysfunction in the period prior to hospitalization. She had no prior history of autoimmune disease. Family history was negative for thyroid disease or systemic autoimmune disease. Review of systems was negative for the involvement of other organ systems. Systemic examination was notable for the presence of confusion and lack of orientation to time but with no focal neurological

**Citation:** Keerthana Haridas. Late manifestation of Immunotherapy induced hypothyroidism with high antibody titers. *J Clin Med Img Case Rep.* 2022; 2(4): 1201.

deficits. No thyromegaly was noted

The patient was found to be hyponatremic (Na 127) but with no other metabolic abnormalities revealed. TSH was measured as part of the work-up for altered mental status. Patient's TSH was found to be elevated at 24.479. Prior TSH levels were measured as part of a routine health maintenance visits and noted to be 1.2 in November 2019. No measurements of TSH were performed after this date, prior to the above hospitalization. Thyroid function tests done following discovery of elevated TSH further revealed TT4 of 3.3mcg/dl (5-12.2) with FT4 of 0.61ng/dl(0.8-1.5), FT3 of 1.64pg/ml(2.5-3.9). Anti TPO antibodies were elevated to 7516.5IU/ml (0-5.6) with anti thyroglobulin antibodies elevated to 49.7U/ml (0-4.1). Ultrasound of the thyroid gland was performed revealing diffusely heterogeneous thyroid gland.

Patient underwent CT head, notable for hyperdense foci concerning for metastases in the brain, confirmed with MRI brain revealing metastatic disease involving bilateral hemispheres of the cerebrum, the cerebellum and the brainstem. The pituitary gland appeared normal on imaging. MRI spine revealed metastatic lesions in cervical and thoracic regions of the vertebral bodies and spinal cord. Cerebral metastatic disease was deemed the most likely cause of the patient's encephalopathy. She was started on intravenous Dexamethasone and was treated with whole brain and spine radiation. The Endocrinology team was consulted for evaluation and management of abnormal TFT. Patient's Myxedema score was calculated and found to be 20(10 points for lethargy, 10 for hyponatremia), lowering the likelihood of myxedema coma. Patient was determined to have grade 2 thyroiditis mediated hypothyroidism and was initiated on Levothyroxine 50mcg daily (1.3mcg/kg) while Atezolizumab was continued in keeping with guidelines for management of grade 2 adverse effects. It would be necessary to exclude adrenal insufficiency and hypophysitis as other closely related endocrine adverse effects of ICPI; however the patient had been on oral corticosteroids since September 2020 which precluded measurement of hormone levels in the hypothalamic- pituitary- adrenal axis. Repeat TSH about 10 days following initial measurement of TSH was 11.353 and patient was discharged on LT4 50mcg daily. Patient was scheduled for outpatient Endocrine follow up in 4-6 weeks.

## Discussion

Immunotherapeutic agents block various cascades responsible for suppressing immune responses [1, 2]. One of these cascades involves the CTLA-4 protein, ordinarily expressed on the surface of the Regulatory T cells (T reg). Its recruitment to the surface of other cells, like the CD4+ Helper T cells is increased by the activation of the immune system by antigens presented by the antigen presenting cells(APCs). Once recruited, it competes with ligands on the APC, inhibiting their binding with activatory immune receptors like CD28 or the T Cell Receptor on these cells. This, in turn, inhibits downstream pro- inflammatory immune responses. It also triggers inhibitory immune pathways and the production of anti-inflammatory cytokines [1]. Another cascade involves the PD-1 checkpoint,

which when bound to by its ligand PD-L1, suppresses intracellular gluconeogenesis thus preventing cell survival, proliferation and the production of pro-inflammatory cytokines [1]. Immune checkpoint inhibitors thus mask the immune inhibitory arms in the body and lead to an upregulation of immune mediated inflammation, causing immune related adverse effects, in addition to tumor cell recognition and death.

Thyroid dysfunction in the setting of treatment with immune checkpoint inhibitors could be secondary to immune hypophysitis, presenting as central hypothyroidism or primary hypothyroidism resulting from autoimmune thyroid dysfunction [1, 2, 3]. Routine measurement of thyroid function tests to explore the functioning of the pituitary- thyroid axis helps differentiate between the two. Central hypothyroidism presents with decreased thyroxine and triiodothyronine levels with low-normal TSH, in comparison to elevated TSH levels encountered in primary hypothyroidism [1, 2, 3] Primary thyroid dysfunction varies between being the most common and the second most common endocrine adverse effect caused by immune checkpoint inhibitors [1, 2, 3, 4]. In a meta- analysis of 38 randomized controlled trials, the overall incidence of hypothyroidism with ICPI therapy was estimated by a mixed-effects model to be around 6.6% and that of hyperthyroidism to be around 2.9%. The highest incidences of both types of dysfunction were noted among those treated with combination anti CTLA-1 plus anti PD-1 therapy (13.2% with ipilimumabnivolumab), followed by monotherapy with anti-PD-1 agents (7.0%) [4]. A possible explanation for this disparity may be that monotherapy may be associated with a milder and more short lived thyrotoxicosis phase, increasing the likelihood that it may be missed in early thyroid function tests [4]. It is also not clearly known why there are higher rates of thyroid dysfunction in patients on anti-PD-1 therapy in comparison with other ICPI monotherapy agents. However, it is known that normal thyroid tissue expresses both PD-L1 and PD-L2 molecules [4]. Thus, antiCTLA4 therapy allows immune regulation through the preserved pathway mediated by PD and its ligands. In addition, blockage of a single PD ligand (PD-L1) allows the remaining PD-L2 ligand to bind with the PD-receptor and activate the downstream pathway for immune suppression [4] of note, Grave's disease post ICPI therapy is very rare, with less than five known cases documented [1]. The most common symptoms of hyperthyroidism were weight loss, anorexia and palpitations while those of hypothyroidism were weight gain and fatigue. Both thyroid storm and myxedema coma are very infrequently reported [1, 2, 5].

Thyroid dysfunction can occur after a single dose of ICPI therapy or as late as many years after therapy although the median time from initiation of the ICPI to the detection of thyroid dysfunction ranged from half a month to 4 months. A study by Lee et al [5] noted that the median time to onset of hypothyroidism was longer than that to thyrotoxicosis (63 days versus 21 days respectively) indicating that thyrotoxicosis may be an initial transient phase in destructive thyroiditis. Around 80% of patients detected to develop thyrotoxicosis went on to develop hypothyroidism during the course of the study [5]. In

our patient, hypothyroidism was first detected 6 months after initiation of ICPI and after multiple doses were received, although TSH was not measured just prior to the initiation of therapy or after the initiation of therapy, prior to this hospitalization.

The mechanism of thyroid dysfunction caused by the use of immune checkpoint inhibitors includes immune mediated inflammation and destruction of the thyroid gland [1, 2, 3]. Delivanis et al. [8] performed flow cytometric analysis on the serum of patients with Pembrolizumab induced thyroiditis, revealing an increased number of circulating CD56+CD16+ natural killer cells, CD14+CD16+ monocytes and an elevated HLA DR surface expression in the inflammatory intermediates. Torimoto et al. [6] performed similar studies using the serum of patients treated with PD-1 inhibitor, Nivolumab and found an increased percentage of follicular T helper cells, in keeping with the hypothesis that anti-PD-1 treatment leads to the inhibition of downstream of immune suppressive pathways in these cells, enhancing their proliferation and contributed to the development of thyroiditis.

The role of autoantibodies including anti-TPO or anti-TG antibodies in the pathogenesis of thyroid dysfunction is not clearly known. Patients with clinical and biochemical evidence of thyroid dysfunction may have undetectable antibody levels while those with drastically elevated titres of autoantibodies may not have any evidence of thyroid dysfunction [1]. It is thus not clearly known whether these antibodies do mediate thyroiditis or whether the culprit antibodies responsible for the same have not been detected and measured as yet [1]. In addition, it is also unclear whether those with elevated antibody titers at baseline are at an increased risk of developing thyroid endocrinopathy post ICPI treatment, with studies revealing data for and against this hypothesis [1]. Our patient had drastically elevated titres of anti-Thyroid Peroxidase antibodies as well as elevated levels of Anti thyroglobulin antibodies, with no prior evidence of elevated antibody titers prior to immunotherapeutic treatment. She was unaware of elevated antibody titers in her family members.

Measurement of baseline TSH prior to the initiation of treatment with immune checkpoint inhibitors and before each infusion for at least 5 cycles is recommended. However, the routine measurement of thyroid autoantibodies or imaging of the thyroid gland is not recommended [1]. It is essential to differentiate between central and primary hypothyroidism when detected as central hypothyroidism may be the first detected abnormality in immune hypophysitis, necessitating evaluation of coexisting central adrenal insufficiency and hypogonadotropic hypogonadism. In cases of concurrent hypoadrenalism and central hypothyroidism, patients must be treated with steroid replacement prior to thyroid hormone replacement to avoid precipitation of an adrenal crisis. Therapy with Levothyroxine may be started at a lower than conventional dose of around 0.8mcg/kg in young patients without cardiovascular disease, and then modified as needed [1]. This is done because thyroidal illness in this setting is often transient and the dose can always be titrated upwards as necessary [1]. A study by Roos et al found no significant differences in symptoms or quality of life with the above dose versus conventional dose of thyroid hormone replacement [9].

In case of thyrotoxicosis, symptomatic treatment is provided

using beta blockers, which can be terminated when thyrotoxicosis improves. Anti-thyroid drugs are not used unless Grave's disease is detected since the underlying pathophysiology for thyrotoxicosis is leakage of thyroid hormone secondary to inflammatory thyroiditis, rather than an autonomous increase in hormone production [1]. It is important to carry out serial measurement of thyroid function tests every 3-6 weeks to monitor for recovery of thyroid function and possible transition to hypothyroidism [1].

The degree of thyroid dysfunction is classified into 5 grades based on the severity of symptoms and their effect on quality of life of patients. ICPI therapy should be modified on the basis of the grade of thyroid dysfunction with the following broad principles for management:

1. grade 1 or 2: ICPI therapy should be continued with close follow-up and monitoring of TFT, with symptomatic treatment as needed
2. grade 3: ICPI therapy should be interrupted with symptomatic treatment as appropriate and treatment re-initiated upon resolution of dysfunction
3. grade 4: ICPI should be permanently withheld and treatment of thyroid dysfunction provided

While there is conflicting evidence on whether the occurrence of immune endocrinopathies in response to ICPI therapy are associated with improved efficacy of immunotherapy in patients, a meta-analysis of 30 studies showed that the occurrence of particularly endocrine and dermatologic irAEs were associated with improved efficacy of treatment [7]. The occurrence of particularly thyroid dysfunction after immunotherapy has been associated with improved OS in patients [10].

## Conclusion

A high index of suspicion must be present for the development of immune endocrinopathies including thyroid dysfunction in patients treated with immunotherapy given that they may be life threatening if missed. Endocrinologists and oncologists must work hand in hand for a holistic multi-disciplinary management of the patient. Patients and their families should be educated regarding the possible occurrence of endocrine dysfunction, their prompt recognition and management. No studies have been carried out, to our knowledge, to detect the presence of genetic polymorphisms in checkpoint proteins CTLA4/PD-1/PDL-1 in these patients. This may help predict an increased likelihood of developing thyroid dysfunction in these patients upon treatment with immunotherapeutic agents. There is thus a need for studies to be carried out, especially to determine risk factors and predictors, of endocrinopathies so that appropriately tailored agents may be selected for cancer therapy.

## References

1. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. *Endocr Rev.* 2019 Feb 1; 40(1): 17-65. [PMID: 30184160; PMCID: PMC6270990 DOI: 10.1210/er.2018-00006].
2. Ferrari SM, Fallahi P, Galetta F, Citi E, Benvenega S, Antonelli A. Thyroid disorders induced by checkpoint inhibitors. *Rev*

Endocr Metab Disord. 2018 Dec; 19(4): 325-333. [PMID: 30242549 DOI: 10.1007/s11154-018-9463-2].

3. Elia G, Ferrari SM, Galdiero MR, Ragusa F, Paparo SR, Ruffilli I, et al. New insight in endocrine-related adverse events associated to immune checkpoint blockade. *Best Pract Res Clin Endocrinol Metab.* 2020 Jan; 34(1): 101370. [PMID: 31983543 DOI: 10.1016/j.beem.2019.101370] [Epub 2019 Dec 11].

4. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, Tolaney SM. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Metaanalysis. *JAMA Oncol.* 2018 Feb 1; 4(2): 173-182. [PMID: 28973656; PMCID: PMC5838579 DOI: 10.1001/jamaoncol.2017.3064].

5. Lee H, Hodi FS, Giobbie-Hurder A, Ott PA, Buchbinder EI, Haq R, et al. Characterization of thyroid disorders in patients receiving immune checkpoint inhibition therapy. *Cancer Immunol Res.* 2017; 5(12): 1133-1140.

6. Torimoto K, Okada Y, Nakayamada S, Kubo S, Tanaka Y. Anti-PD-1 Antibody Therapy Induces Hashimoto's Disease with an Increase in Peripheral Blood Follicular Helper T Cells. *Thyroid.* 2017 Oct; 27(10): 1335-1336.

7. Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. *BMC Med.* 2020 Apr 20;18(1):87. [PMID: 32306958; PMCID: PMC7169020 DOI: 10.1186/s12916-020-01549-2].

8. Delivanis DA, Gustafson MP, Bornschlegl S, Merten MM, Kottschade L, Withers S, Dietz AB, Ryder M. Pembrolizumab-induced Thyroiditis: Comprehensive Clinical Review and Insights Into Underlying Involved Mechanisms. *J Clin Endocrinol Metab.* 2017 Aug 1; 102(8): 2770-2780.

9. Roos A, Linn-Rasker SP, van Domburg RT, Tijssen JP, Bergh-

out A. The starting dose of levothyroxine in primary hypothyroidism treatment: a prospective, randomized, double-blind trial. *Arch Intern Med.* 2005 Aug 8-22; 165(15):1714-20.

10. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Hellmann MD Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann Oncol.* 2017 Mar 1; 28(3): 583-589.