Endocrinopathies Associated with Immune Checkpoint Inhibitors

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About the Author

Dr. Irena Druce completed her studies, including a Masters' in Cellular and Molecular Medicine and her medical education, at the University of Ottawa. She practices in the community and as a part-time associate with The Ottawa Hospital. She is an assistant professor with the Department of Medicine at the University of Ottawa and has collaborated with medical oncology on research into endocrine side effects of immune checkpoint inhibitor therapy. Her other clinical interests include type 2 diabetes and transgender medicine.

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Introduction

Immune checkpoint receptors are expressed by cells of the immune system and lead to reduced or absent function, which physiologically limits autoimmunity. These receptors are also exploited by malignant cells to maintain immune tolerance and evade destruction. Monoclonal antibodies targeting immune checkpoints have revolutionized oncology, with potential long-lasting clinical response, even in the setting of metastatic solid tumors. For example, in the past, metastatic melanoma signalled certain death; now, remission is possible.[1]

The primary targets of current pharmacotherapy are cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1) and its ligand (PD-L1). Today, half of all patients with metastatic disease are eligible to receive immune checkpoint inhibitor (ICI) therapy. As of December 2021, there were eight approved agents available for 17 malignancies, and more than 1,000 clinical trials have been conducted to explore these agents in adjuvant and maintenance settings.[1,2]

The immune activation that underlies ICI therapy and the persistence of clinical response beyond the pharmacologic half-life also explain the toxicities that have been observed.[1] Immune-related adverse events (irAEs) from ICI therapy have been shown to occur in virtually every organ system. They manifest at varying times during treatment, sometimes occurring after its discontinuation. Interestingly, the presence of these adverse events (AEs) is related to the immune system's degree of self-tolerance and predicts patient response to this treatment modality.[3]

Endocrinopathies are some of the most common irAEs, occurring in 15–40% of patients; however, they have posed challenges for clinicians as they are difficult to diagnose due to diverse and non-specific manifestations.[1-4] In contrast to other irAEs, endocrinopathies do not respond to high-dose glucocorticoids and they are permanent. Steroid treatment has been shown to have no effect on the disease severity or the likelihood of resolution.[5,6] Fortunately, when diagnosed appropriately, ICI-associated endocrinopathies are easy to treat, do not necessitate treatment discontinuation, and have an excellent prognosis.[7]

ICI-Associated Hypophysitis

Hypophysitis is one of the more common and most life-threatening irAEs and can affect any, and often multiple, anterior pituitary cell lineages (**Figure 1**). ICI-associated diabetes insipidus (DI) resulting from antidiuretic hormone deficiency has been noted only in case reports. Hypophysitis is noted most frequently with CTLA-4 therapy (either alone or in combination with programmed cell death protein 1/ligand 1 [PD-1/L1]), seen in up to 10% of treated patients. It has also

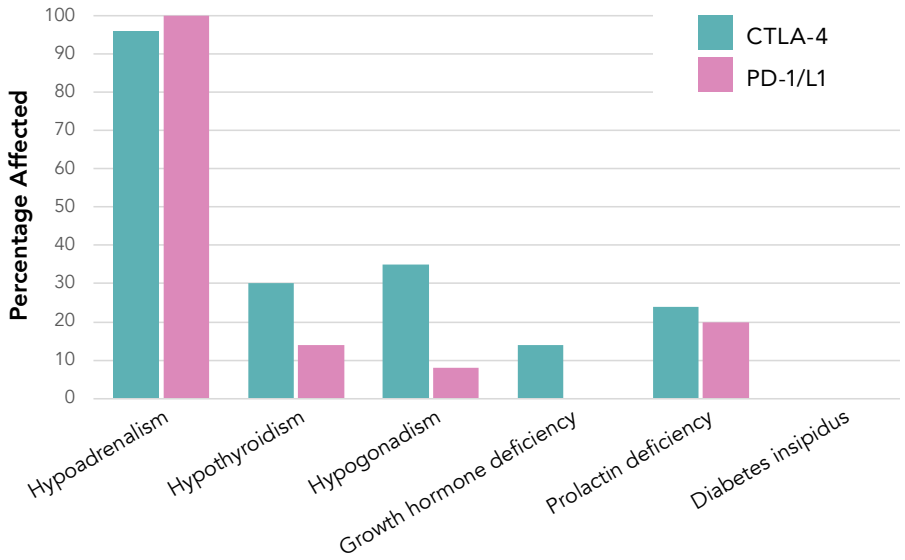

Figure 1: Percentage of patients presenting with deficiency in specific cell axes in ICI-associated hypophysitis. *Data adapted from Faje and Druce.*[8,9]

been shown to occur with PD-1/L1 monotherapy, although more rarely, with a reported incidence of 1–3% (Table 1). The clinical presentation differs based on the causative agent.

CTLA-4-associated hypophysitis occurs early in the treatment course, typically within 9–12 weeks, and most commonly causes concurrent central hypoadrenalism and central hypothyroidism. The underlying mechanism has been proposed to be a hypersensitivity type II reaction with lymphocytic infiltration into the pituitary gland noted on pathology. This is very similar to autoimmune hypophysitis which was a known, albeit rare, entity prior to the ICI-era.

Hypophysitis due to PD-1/L1 therapy occurs later in the treatment course, generally following 20 weeks, and almost universally affects adrenocorticotropic hormone (ACTH) secretion leading to hypoadrenalism; it rarely affects other cell lineages.[4,8,9] The mechanism for PD-1/L1-associated hypophysitis is not yet elucidated.

There is no consensus on asymptomatic screening for hypophysitis, more specifically ACTH deficiency, in ICI-treated patients. This may be due to the complexity of obtaining morning serum cortisol measurements, as well as correct interpretation while accounting for confounding by the frequent use of glucocorticoids in this population.[8] Some practitioners support routine screening in at least CTLA-4-containing regimens, based on the increased incidence; however, there are no clear guidelines concerning how to measure and interpret cortisol values. Debate exists, even among endocrinologists, regarding what cut-off values should be used for interpretation of serum cortisol.[9] Measuring ACTH is not practical due to the long turn-around time for this assay in most institutions.

ACTH deficiency is acutely life-threatening and its manifestations, namely malaise, nausea and hypotension are, unfortunately, common in patients receiving systemic therapy for cancer. Late diagnosis is a realistic possibility and it can have a profound impact on patient morbidity and mortality, supporting the implementation of asymptomatic screening.[4,9] Clinicians are encouraged to have a high index of suspicion for pituitary dysfunction, and should be aware of the need for this condition to be assessed and treated by oncologists and endocrinologists collaboratively.

In addition, imaging the pituitary gland in ICI-associated hypophysitis is not standard, as the presence of inflammation and stalk thickening on magnetic resonance imaging (MRI) does not predict the severity or course of the condition. Imaging should be considered if pituitary metastases are on the differential.[4,7]

ICI-associated hypophysitis is treated by replacing the target hormones, as with any other etiology of hypopituitarism. Priority should be given to replacing the adrenal and thyroid axes. Sex hormone replacement can be considered if the underlying disease has a reasonable prognosis, and growth hormone replacement therapy (GHRT) is contraindicated in the setting of active malignancy.[4,7,10]

ICI-Associated Thyroid Disease

Primary thyroid dysfunction is the most common endocrinopathy noted with ICI therapy and typically presents within six weeks of treatment. It can, however, occur at any time during therapy and these factors have led to screening serum thyroid stimulating hormone (TSH) as routine practice.[4] The incidence varies by treatment; the clinical data has shown 5% in CTLA-4 monotherapy, 10% in PD-1/L1 monotherapy, and up to 20% for patients treated with combination therapy.[4,11]

The most common presentation is destructive, painless thyroiditis, where transient hyperthyroidism leads to permanent hypothyroidism in virtually 70% of cases within approximately six weeks. This time course is more rapid than that of non-ICI-associated thyroiditis and is unaffected by the use of glucocorticoids. It is possible that the

Endocrinopathy	Incidence (%)			Onset (Median Weeks)		
	CTLA-4	*PD-1/L1*	*Combo*	*CTLA-4*	*PD-1/L1*	*Combo*
Hypophysitis	9%	1-3%	10.5%	9-12	26	9-12
Primary thyroid						
Thyroiditis	1-5%	5-10%	2-10%	6+	6+	6+
Hypothyroidism	2-5%	3-10%	5-23%	6+	6+	6+
Graves disease	-	-	-	-	-	-
Autoimmune diabetes	-	0.2-5%	0.6%	-	Within 15	-
Primary adrenal	0.3-2%	0.3-4%	1-3%	-	-	-

Table 1: Summary of incidence and timing of onset of ICI-associated endocrinopathies based on treatment regimen. *Data adapted from Wright and Barroso-Sousa.*[4,11]

incidence of self-limited thyroiditis is much higher as it is largely subclinical. Graves disease is rare and has been noted in case reports due to the presence of orbitopathy.[4]

There is no clinical utility in measuring thyroid-stimulating hormone (TSH)-receptor antibodies. Other anti-thyroid antibodies, such as anti-thyroid peroxidase and anti-thyroglobulin, are often absent in patients manifesting with ICI-associated thyroid dysfunction. In patients with pre-existing anti-thyroid antibodies, there is a higher risk to develop irAEs; however, there is no correlation with disease severity.[4,12] The pathophysiology of this endocrinopathy remains under study; however, the PD-1/L1 pathway is integral in T-cell function, which is linked to the pathophysiology of Hashimoto thyroiditis.[13]

Recommendations for monitoring and treatment of ICI-associated primary thyroid dysfunction are unanimous and clear: Free hormones should be measured where an abnormal TSH is noted, and levothyroxine therapy should be initiated when the TSH is >10mIU/mL at a standard dosing of 1.6 mcg/kg (less in the elderly and frail), followed by biochemical reassessment in six weeks.[4,7]

ICI-Associated Diabetes Mellitus

The next most notable ICI-associated endocrinopathy is autoimmune diabetes (ICI-DM). Its incidence is rare; it occurs in less than 0.2–5% of patients; however, its presentation can be dramatic with rapid autoimmune destruction of β-cells and up to 70% of patients presenting with fulminant ketoacidosis.[4] Due to its rapid presentation, screening with A1c may not be useful and random plasma or capillary blood glucose monitoring should be used for routine screening.[7] In a clinical trial, the majority of patients, over 70%, presented in the first three months of initiating ICI therapy; however, the latest presentation reported was 15 months.[14] Fewer than 50% of patients were noted to have islet-antibodies; however, the patients who had positive antibodies developed ICI-DM at an earlier point. More than 97% of cases of ICI-DM have been noted in patients on PD-1/L1 therapy and this pathway has been observed to be important to the development of diabetes mellitus in mouse models.[4] In addition, genetic factors are likely to contribute to the development of ICI-DM, with classic HLA haplotypes linked with classic type 1 diabetes (DR3-DQ2 and DR4-DQ8) being over-represented in ICI-DM, along with a strong association with ICI-DM and HLA-DR4.[15]

The administration of high-dose glucocorticoids has not been shown to provide any benefit in ICI-DM; this condition should be treated with subcutaneous insulin.[7] It should also be noted that the patient population requiring ICI therapy is at higher risk of developing pre-existing type 2 diabetes and the frequent use of glucocorticoids in this population may exacerbate glycemic control. Patients should be screened for pre-existing diabetes prior to initiating treatment.

Additional ICI-Associated Endocrinopathies

Other endocrinopathies are rare. Primary adrenal insufficiency has been noted to occur with an incidence of 0.2–0.5% and is rarely associated with the presence of anti-adrenal antibodies.[11] Hypoparathyroidism, DI and ACTH-dependent Cushing disease have been noted in case reports; however, the link to ICI therapy is questioned.[4] In these instances, causality is unimportant as, ultimately, the treatment is unaffected.

Where ICI therapy is making the biggest impact on endocrinologists is with the increased incidence of hypophysitis and autoimmune diabetes, which require expert diagnosis and treatment.

Summary

ICIs have ushered in a new era in cancer treatment, but they are still in their infancy. Most notably, the first ICI was FDA approved in recent years, in 2011. Extensive research is needed to elucidate the mechanisms that underly the irAEs so that patients can be properly diagnosed and treated. Future research may also allow the identification of high-risk patients requiring closer surveillance.

With regard to ICI-associated endocrinopathies, at this time, clinicians must rely on their clinical acumen and routine screening. A basic screening algorithm is proposed in Figure 2 and could be adapted to individual institutional needs. Asymptomatic screening should be most intense during treatment when the incidence of onset is highest. It is important to note that irAEs can occur after treatment discontinuation and clinical vigilance must persist. Patients with any prior exposure to ICI therapy should be identified in their medical record and should have biannual clinical review with targeted endocrine testing as indicated.

With ICI therapy, patients could potentially be cured of their malignancy, and the possibility exists that they could be discharged to their primary care providers (PCPs), who would then assume the responsibility for ongoing surveillance. Knowledge dissemination, a multidisciplinary approach and collaboration between specialists will be key on the path forward.

Prior to treatment	Serum/capillary glucose
	TSH
During treatment Q1–2 cycles	TSH
	Serum/capillary glucose
	Morning serum cortisol*
After treatment discontinuation	Clinical assessment every 6 months, investigations as clinically indicated

* *Consider for all patients but at minimum those exposed to CTLA-4 agents.*

Figure 2: Basic algorithm for screening of ICI-associated endocrinopathies.

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References

1. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol. 2022 Apr;19(4):254-67.
2. Esfahani K, Meti N, Miller WH, Hudson M. Adverse events associated with immune checkpoint inhibitor treatment for cancer. CMAJ. 2019 Jan 14;191(2):E40-6.
3. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer. 2019 Dec;7(1):1-1.
4. Wright JJ, Powers AC, Johnson DB. Endocrine toxicities of immune checkpoint inhibitors. Nat Rev Endocrinol. 2021 Jul;17(7):389-99.
5. Faje AT, Lawrence D, Flaherty K, Freedman C, Fadden R, Rubin K, Cohen J, Sullivan RJ. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. Cancer. 2018 Sep 15;124(18):3706-14.
6. Ma C, Hodi FS, Giobbie-Hurder A, Wang X, Zhou J, Zhang A, Zhou Y, Mao F, Angell TE, Andrews CP, Hu J. The Impact of High-Dose Glucocorticoids on the Outcome of Immune-Checkpoint Inhibitor–Related Thyroid DisordersManagement of ICI-Induced Thyroiditis. Cancer Immunol Res. 2019 Jul 1;7(7):1214-20.
7. Husebye ES, Castinetti F, Criseno S, Curigliano G, Decallonne B, Fleseriu M, Higham CE, Lupi I, Paschou SA, Toth M, van der Kooij M. Endocrine-related adverse conditions in patients receiving immune checkpoint inhibition: an ESE clinical practice guideline. Eur J Endocrinol. 2022 Dec;187(6):G1-21.
8. Faje A, Reynolds K, Zubiri L, Lawrence D, Cohen JV, Sullivan RJ, Nachtigall L, Tritos N. Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis. Eur J Endocrinol. 2019 Sep;181(3):211-9.
9. Druce I, Tawagi K, Shaw JL, Ibrahim A, Lochnan H, Ong M. Routine Screening for Central and Primary Adrenal Insufficiency during Immune-Checkpoint Inhibitor Therapy: An Endocrinology Perspective for Oncologists. Curr Oncol. 2022 Jul 2;29(7):4665-77.
10. Girotra M, Hansen A, Farooki A, Byun DJ, Min L, Creelan BC, Callahan MK, Atkins MB, Sharon E, Antonia SJ, West P. The current understanding of the endocrine effects from immune checkpoint inhibitors and recommendations for management. JNCI Cancer Spectr. 2018 Jul;2(3):pky021..
11. 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 meta-analysis. JAMA Oncol. 2018 Feb 1;4(2):173-82.
12. Kobayashi T, Iwama S, Yasuda Y, Okada N, Tsunekawa T, Onoue T, Takagi H, Hagiwara D, Ito Y, Morishita Y, Goto M. Patients with antithyroid antibodies are prone to develop destructive thyroiditis by nivolumab: a prospective study. J Endocr Soc. 2018 Mar;2(3):241-51.
13. Zhan L, Feng HF, Liu HQ, Guo LT, Chen C, Yao XL, Sun SR. Immune checkpoint inhibitors-related thyroid dysfunction: epidemiology, clinical presentation, possible pathogenesis, and management. Front Endocrinol. 2021 Jun 10;12:649863.
14. Akturk HK, Kahramangil D, Sarwal A, Hoffecker L, Murad MH, Michels AW. Immune checkpoint inhibitor-induced type 1 diabetes: a systematic review and meta-analysis. Diabet Med. 2019 Sep;36(9):1075-81.
15. Tsang VH, McGrath RT, Clifton-Bligh RJ, Scolyer RA, Jakrot V, Guminski AD, Long GV, Menzies AM. Checkpoint inhibitor–associated autoimmune diabetes is distinct from type 1 diabetes. J Clin Endocrinol Met. 2019 Nov;104(11):5499-506.