Endotext

IMMUNE CHECKPOINT INHIBITORS RELATED ENDOCRINE ADVERSE EVENTS

Ghada Elshimy, MD, Department of Internal Medicine, Division of Endocrinology, Diabetes, and Metabolism, Augusta University, Augusta, GA, USA 39012. gelshimy@augusta.edu
Rishi Raj, MD, Department of Internal Medicine, Division of Endocrinology, Diabetes, and Metabolism, Pikeville Medical Center, Pikeville, KY, USA 41501. rishiraj91215@gmail.com
Halis Kaan Akturk, MD, Department of Medicine, Division of Endocrinology, Barbara Davis Center for Diabetes, University of Colorado, School of Medicine, Aurora, CO, USA. Halis.akturk@cuanschutz.edu
Aleksandra Schriber, MD, Division of Internal Medicine, University of Arizona College of Medicine-Phoenix. Phoenix, AZ, USA 85004. Alexandra.schriber@bannerhealth.com
Nuria Sisterna, MD, Division of Internal Medicine, University of Arizona College of Medicine-Phoenix. Phoenix, AZ, USA 85004. Nuria.cisterna@bannerhealth.com
Iram Ahmad, MD, Department of Medicine, University of Arizona College of Medicine-Phoenix. Phoenix, AZ, USA 85004. Division of Endocrinology, Banner-MD Anderson Cancer Center, Gilbert, AZ. Iram.ahmad@bannerhealth.com
Aasems Jacob, MD, Department of Internal Medicine, Division of Hematology and Oncology, Pikeville Medical Center, Pikeville, KY, USA 41501. aasemsj@gmail.com
Aaron W. Michels, MD, Department of Medicine, Division of Endocrinology, Barbara Davis Center for Diabetes, University of Colorado, School of Medicine, Aurora, CO, USA. Aaron.michels@cuanschutz.edu
Ricardo Correa, MD, Division of Endocrinology, Phoenix VAMC and University of Arizona College of Medicine-Phoenix. Phoenix, AZ, USA 85012. riccorrea20@gmail.com

Received January 20, 2022

ABSTRACT

Immune checkpoint inhibitors (ICIs) are currently used for the treatment of various types of cancers. Despite the important clinical benefits, these medications can lead to a spectrum of side effects called immune-related adverse events (irAEs). Endocrine irAEs are among the most common irAEs that have been reported in clinical trials and post-marketing settings with an overall incidence of around 10% of patients treated with ICIs. These include hypothyroidism, hyperthyroidism, hypophysitis, primary adrenal insufficiency, insulin-deficient diabetes mellitus, hypogonadism, hypoparathyroidism, hypocalcemia, and other less commonly reported side effects. The symptoms can sometimes be nonspecific but life-threatening. Hence, physicians should be aware of the endocrine irAEs which can occur anytime during treatment or even after discontinuation of the medications. In this chapter, we will be discussing in detail the ICI-related endocrine irAEs and their management. In addition, we will be suggesting an algorithm to be used in the clinical setting for screening and monitoring of the endocrine iRAEs.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are currently approved by the US Food and Drug Administration (FDA) for the treatment of various types of cancers and have significantly improved clinical outcomes and survival. Antigen-presenting cells (APCs) process and express antigens (including tumor antigens) on major histocompatibility complexes recognized by receptors on T cells, which then stimulates a cascade either to kill the cell expressing the antigen (via CD8+

effector/cytotoxic T cells) or recruit other components of the immune system (via CD4+ helper cells) (1). Many of the ligands presented by the APCs can bind to multiple receptors and deliver stimulatory or inhibitory signals, the latter being referred to as immune checkpoints. Various ligand-receptor interactions between antigen-presenting cells and T cells regulate the T cell response to the antigen (Figure 1). Agonists of stimulatory receptors or antagonists of inhibitory signals can result in amplification of antigen-specific T-cell responses (2). Cancer cells can develop tolerance to the immune system by upregulating the expression of immune checkpoint molecules like programmed cell death ligand (PD-L1) leading to peripheral T cell exhaustion or lose surface antigen expression leading to immunologic escape. ICIs help overcoming this tolerance by inhibiting the checkpoints and these inhibitory compounds currently used in pharmacologic intervention target three ligands/receptors- CTLA-4, PD-1, and PD-L1 (3).

Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) Inhibitors

CTLA-4 was first described by Leach et. al. in 1996 as a receptor on T cells (3), where it acts as a physiologic brake on the T-cell activation. It competes with the CD28 stimulatory receptor present on T cells (1). Both bind CD80 and CD86 ligands (also known as B7.1 and B7.2 respectively, collectively as B7) seen on APCs, but CTLA-4 has a 500-2500 times higher affinity for these ligands than CD28 does. Blocking CTLA-4: B7 interactions favors CD28:B7 interactions, which results in proliferation of T cells, increased T cell survival, activation of T effector cells, and increased diversity of T cell responses on tumors. This is the basis of CTLA-4 inhibitor therapy with ipilimumab (trade name Yervoy) and tremelimumab (4, 5).

Programmed Death-1 (PD-1) and Programmed Death-Ligand 1 (PD-L1) Inhibitors

PD-1 receptors on the T cell interact with PD-L1 (another member of the B7 family) and inhibit T-cell expression and decrease expression of proinflammatory cytokines such as interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-alpha), and interleukin -2 (IL-2) similar to CTLA-4. PD-L1 is found on leukocytes, nonlymphoid tissue, and tumor cells and modulates CD8+ T cell function (1). PD-L1 is aberrantly expressed on many cancers, including lung, ovary, colon, head and neck, and breast (6) and results in tumor cells evading the immune system (7). Inhibition of PD-1: PD-L1 interaction increases the number of T cells and inflammatory markers at tumor sites, creating an environment more conducive to tumor suppression. Drugs that target PD-1 include pembrolizumab (Keytruda), nivolumab (Opdivo), and dostarlimab (Jemperli) while PD-L1 inhibitors include atezolizumab (Tecentriq), avelumab (Bevancio), and Durvalumab (Imfinzi). PDL-2 is expressed on dendritic cells, monocytes, and mast cells and modulates CD4+ function.

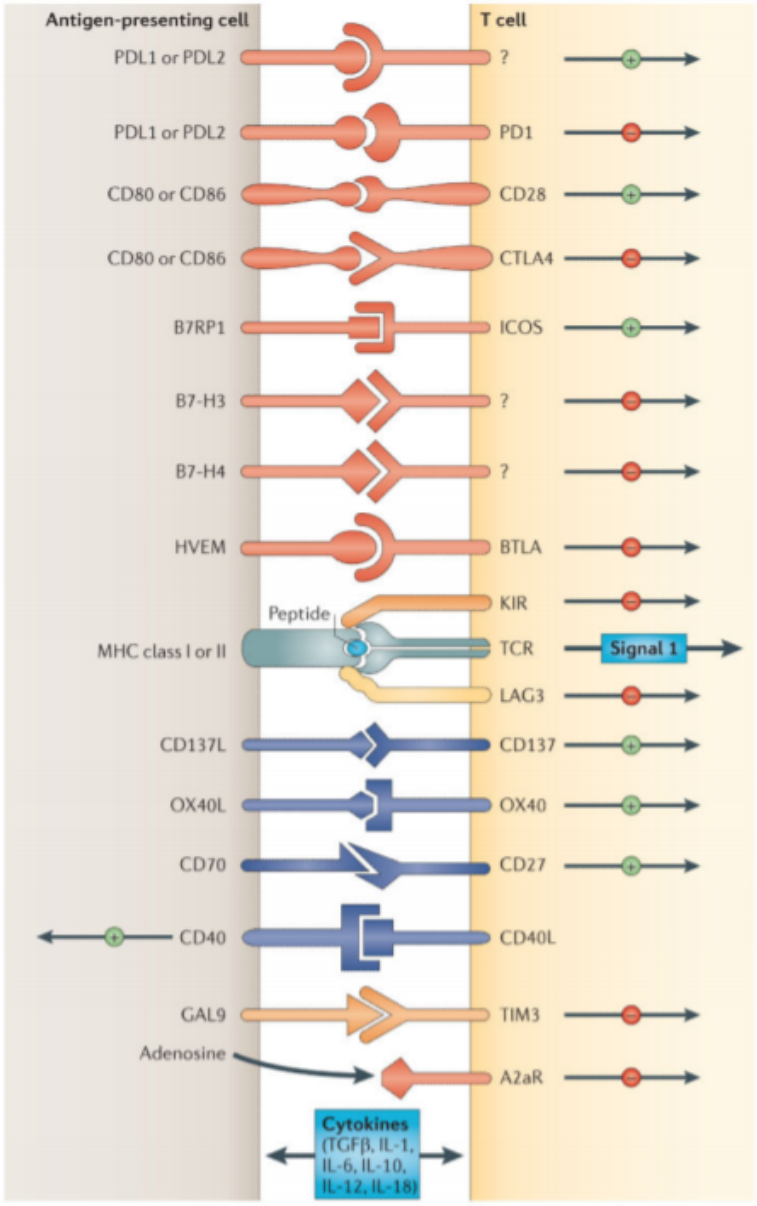

Figure 1. Interactions between antigen-presenting cells (APCs) and T cells that regulate T-cell responses. From DM Pardoll (2)

IMMUNE RELATED ADVERSE EVENTS (irAEs)

Immune checkpoints normally inhibit the function of T cells, which helps prevent autoimmunity but can also benefit cancer cells. ICIs prevent the apoptosis and downregulation of T cells, which allows the immune system to naturally fight malignant cells. Despite the important clinical benefits, this unique mechanism of action itself can lead to a spectrum of side effects called immune-related adverse events (irAEs). Endocrine irAEs are among the most common irAEs that have been reported in clinical trials and post-marketing settings with a meta-analysis of 38 randomized trials showing an overall incidence of endocrinopathies among 10% of patients treated with ICIs (8). These include hypothyroidism,

hyperthyroidism, hypophysitis, primary adrenal insufficiency (PAI), and insulin-deficient diabetes mellitus. Median time to onset of moderate to severe endocrinopathy is 1.75-5 months with ipilimumab and 1.4-4.9 months for any endocrinopathy with PD-1 inhibitors (9, 10). Patients with pre-existing autoimmune disorders are at higher risk of exacerbation of the autoimmune condition as well as development of an unrelated irAEs (11). Multiple large prospective studies and meta-analyses showed that irAEs are associated with improved treatment outcomes suggesting the activated immune system is also concurrently targeting the cancer (12-14). Hence, the general principle of management of irAEs is to control symptoms with minimum amount of immunosuppression. In this article, we will be discussing in detail the ICI-related endocrine irAEs and its management. We will be suggesting algorithm for screening, monitoring and treatment of the patients and we will be listing a summary of the side effects grading system and incidence in different ICI. (Figure 2-4, Table 3-4).

Immune Checkpoint Inhibitor Induced Thyroid Diseases

ICI-mediated thyroid disease is one of the common endocrine irAEs. It can manifest as primary hypothyroidism secondary to destructive thyroiditis or as hyperthyroidism due to Graves' disease.

HYPOTHYROIDISM

ICI-mediated hypothyroidism can present as primary or secondary hypothyroidism (secondary to hypophysitis, which is discussed below). Primary hypothyroidism usually ensues after an occurrence of ICI-induced thyrotoxicosis. In a study by Abdel-Rahman et. al., authors found a higher risk of all-grade hypothyroidism compared to hyperthyroidism associated with ICIs therapy (15).

Incidence

The incidence of hypothyroidism with the use of immune checkpoint inhibitors varies based on the type of immune checkpoint inhibitors used and monotherapy vs combination therapy. In the largest meta-analysis of 38 randomized control trials comprising 7551 patients, the overall incidence of hypothyroidism was found to be 6.6%. The incidence of hypothyroidism ranged from 3.8% with ipilimumab to 13.2% (95% CI, 6.9%-23.8%) with combination therapy (8). Various other studies have also found similar findings of higher incidence of hypothyroidism with the use of PD-1 inhibitors (7-21%) compared to CTLA-4 inhibitor (0-6%) ipilimumab (16).

Pathophysiology

Anti-thyroid antibodies are often absent in ICI-associated hypothyroidism, suggesting a role of cell-mediated rather than humoral autoimmunity (17). In addition, some studies have suggested an increased risk of ICI-induced thyroid dysfunction among patients with pre-existing anti-thyroid antibodies compared to those without these antibodies suggesting unmasking of autoimmune destruction with the use of ICIs (18, 19). The complete pathophysiology behind the development of thyroid dysfunction is not completely understood, but increased cytokine levels following anti-PD1 therapy have been found to correlate with thyroid dysfunction (20). Fine-needle aspiration biopsy obtained during active ICI-induced thyroiditis showed lymphocytic infiltrate along with CD163+ histiocytes (21).

Clinical Characteristics

The median time to thyroid dysfunction following initiation of ICIs is 6 weeks and most of the patients develop biochemical hypothyroidism (22). Nonetheless, thyroid dysfunction can happen at any time during therapy. Most of the patient are asymptomatic or have very few symptoms. Common presenting symptoms include fatigue, depressed mood, mild weight gain, and constipation however with

severe hypothyroidism, the patient can present with altered mental status (23).

Screening and Monitoring

Thyroid function tests should be performed in all the patients receiving ICIs, by measuring TSH (thyroid stimulating hormone) and free T4 (free thyroxine). In the setting of abnormal thyroid function tests, routine monitoring is recommended at 4-6 weeks or more frequently if clinically indicated. However, in presence of normal thyroid function tests, the frequency could be increased to every 12-18 weeks. ICI-induced hypothyroidism is diagnosed by the presence of elevated TSH and decreased free T4. However, TSH is the more sensitive and preferred test. Currently, anti-thyroid antibodies have not been proven to be helpful in the screening and treatment of these patients. For patients who have subclinical hypothyroidism (elevated TSH and normal Free T4), routine monitoring is recommended while continuing treatment with immunotherapy.

Treatment

The diagnosis of primary hypothyroidism is based on elevated TSH (>10 mIU/L) and low free T4 along with clinical symptoms. Once the diagnosis is established, treatment is recommended with levothyroxine supplementation. For young patients with TSH >10 and low free T4, a full replacement dose at 1.6 mcg/kg should be considered. However, in elderly patients or among patients with cardiovascular comorbidities, a lower starting dose of 50 mcg is recommended. The dose should be changed by ~10% every 4-6 weeks to achieve reference range or age-appropriate range TSH and free T4. ICIs are usually continued while treating hypothyroidism with mild to moderate symptoms (24, 25). Although the guidelines to diagnose and treat ICI–associated primary hypothyroidism is well established, the recommendations for the management of patients with subclinical hypothyroidism (mildly elevated TSH with normal free T4) is not well established and should be based on the patient's symptoms, age, and co-morbid conditions (26, 27).

THYROTOXICOSIS

ICI-mediated thyrotoxicosis can present as transient thyrotoxicosis or persistent hyperthyroidism. Transient thyrotoxicosis is far more common among patients treated with ICIs and is often followed by primary hypothyroidism; persistent hyperthyroidism is less frequent. Hyperthyroidism is more commonly reported with combination therapy and is rare with PD-L1 inhibitors. Patients with hyperthyroidism can be symptomatic and need supportive care with beta-blockers and anti-thyroid medications in some cases.

Incidence

The prevalence of ICI-associated transient thyrotoxicosis has varied significantly among the studies and can range from 3.0-9.0% (23, 28) and is followed by primary hypothyroidism (8). The incidence of transient thyrotoxicosis is higher among patients treated with combination therapy compared to monotherapy with anti-PD1 or anti-PD-L1 therapy (23). In the largest to date meta-analysis, the overall incidence of hyperthyroidism was estimated to be 2.9%. The incidence of hyperthyroidism ranged from 0.6% with the PD-L1 inhibitor to 8.0% with combination therapy. Combination therapy was found to have an increased risk of higher-grade hyperthyroidism compared to monotherapy. Moreover, the risk of hyperthyroidism was greater with PD-1 inhibitors compared to PD-L1 inhibitors (8). ICI-induced Graves' disease is extremely rare, with only a few reported cases in the literature (29).

Pathophysiology

The pathophysiology of ICI-thyrotoxicosis remains poorly understood. Autoimmunity is believed to play a critical role in leading to thyroiditis among patients treated with ICIs. In one study, combination ICI therapy (ipilimumab and nivolumab) resulted in a more

robust antibody response compared to monotherapy with nivolumab, leading to faster destruction of the thyroid (30). Moreover, patients with elevated anti-TPO or antithyroglobulin antibodies required a higher dose of levothyroxine compared to those who did not have elevated antibodies. In addition to antibody-mediated thyroid destruction, circulating CD56, CD16, and natural killer cells have been implicated in the development of pembrolizumab-induced thyroiditis in one study (17). Another study found an association between PD-L1 and PD-L2 expression on the thyroid gland and destructive thyroiditis (31). Worsening of pre-existing autoimmune thyroid disease and subclinical hypothyroidism in patients treated with ICIs have also been reported, suggesting synergistic roles of autoimmunity and inflammatory mechanisms (30).

Clinical Characteristics

Most patients with thyrotoxicosis are asymptomatic or present with symptoms such as palpitation, agitation, anxiety, and insomnia (23). Although uncommon, ICI-induced Graves' disease following use of CTLA-4-inhibitor and PD1-inhibitors have also been reported and can be associated with graves orbitopathy (23). Graves' orbitopathy can occur with and without TRAb antibodies among patients treated with ICIs (29). ICI-induced thyroid storm is extremely rare and has only been reported a few times in the literature (32, 33). Toxic autonomous nodules or toxic multinodular goiter is not associated with ICIs and if seen among patients treated with ICIs, should be considered a co-incidental finding (23).

Screening and Monitoring

Screening of ICI-induced thyrotoxicosis is performed by TSH and free T4. Thyrotoxicosis is defined as suppressed TSH and it can either be (i) clinical when free T4 is elevated or (ii) subclinical when free T4 is normal. The most common cause of ICI-induced thyrotoxicosis is thyroiditis, which is due to the destruction of thyroid follicular cells with the release of preformed thyroid hormone. This is often associated with transient thyrotoxicosis and eventually progresses to hypothyroidism in the majority (50 to 90%) of the cases (22, 28). Hence, monitoring of TFTs with TSH and free T4 every 4-6 weeks is recommended. The usual duration of thyrotoxicosis with ICIs is about 4-6 weeks (30, 34) and if thyrotoxicosis persists beyond this period, evaluation for Graves' disease should be considered by checking thyroid-stimulating hormone receptor antibody (TRAb) or thyroid-stimulating immunoglobulin (TSI) or a thyroid uptake scan (28)(Figure 2).

Treatment

For patients with minimal symptoms of thyroiditis-associated thyrotoxicosis, and presence of suppressed TSH and elevated free T4, supportive treatment with non-selective beta-blockers such as propranolol should be considered (24). When propranolol is used, the recommended dose is 10-20 mg every 4 to 6 hours for symptomatic management and until thyrotoxicosis resolves. As most of the time, patients with ICI-induced thyrotoxicosis progress to develop primary hypothyroidism (defined by elevated TSH levels), further treatment with thyroid hormone replacement should be considered. However, in the minority of cases (such as prominent initial symptoms, significantly elevated free T4 levels, signs of Graves' orbitopathy, or persistent thyrotoxicosis), further evaluation and treatment for Graves' disease should be considered (30, 34). Graves' disease should be treated with anti-thyroid medications, radioactive iodine, or surgery depending on the clinical setting and patient preference (35). Rarely, patients can develop thyroid storm and high-dose steroids should be used in conjunction with standard management among these patients (34). If asymptomatic or only mildly symptomatic, continuation of ICIs is recommended (24, 25).

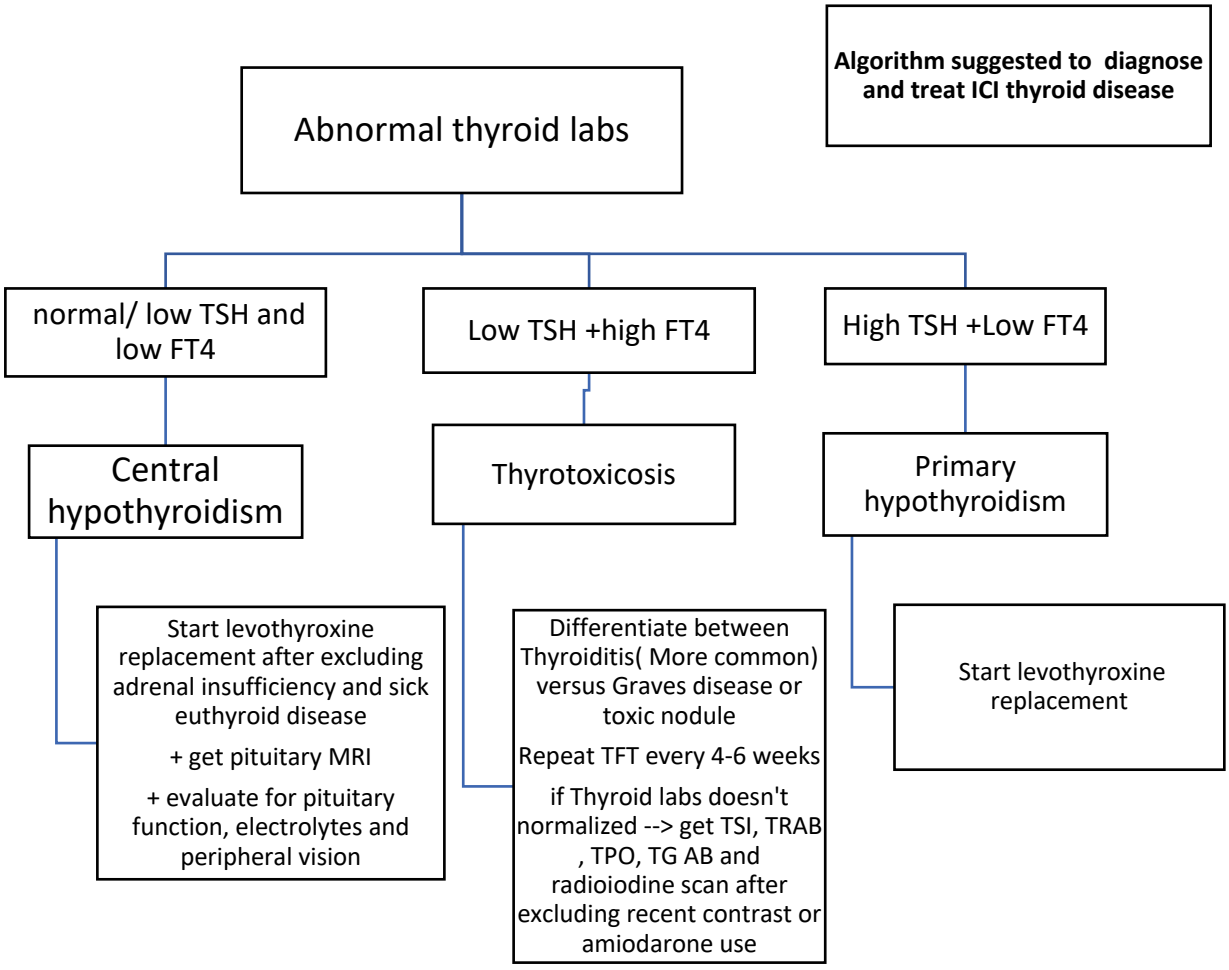

Figure 2. Algorithm suggested to diagnose and treat ICI thyroid disease.

Hypophysitis

Hypophysitis is one of the more common endocrine side effects reported with the use of ICIs particularly with CTLA-4 antibodies and combination therapy including both CTLA-4 and PD1 or PD-L1 inhibitors. It is less likely with PD-1 or PD-L1 inhibitor monotherapy. Hypophysitis is characterized by infiltration and inflammation of the pituitary gland. It can occur in the first few weeks of treatment with frequent hormonal deficiencies at the time of diagnosis. Pituitary enlargement is considered both a highly sensitive and specific indicator of hypophysitis after ruling out metastatic disease. Moreover, the symptoms of hypophysitis can sometimes be non-specific, hence the importance of close monitoring of these patients for early diagnosis and prompt treatment (36, 37).

INCIDENCE

Hypophysitis estimated incidence was one in nine million people per year (38). ICI-induced hypophysitis has been reported in 0-17% of ICI-treated patients. Some studies showed the incidence increased up to 25% while using higher doses of ipilimumab of 10

mg/kg (36, 37, 39). There have been some variations in the observed incidence rate of ICI-induced hypophysitis which has been attributed to not only the dose of the medication but also to the difference in the use, the intensity, and the frequency of hormonal monitoring, in addition to clinical awareness of and suspicion for the condition (37, 40).

Adrenocorticotropic hormone (ACTH) is one of the most common hormone deficiencies in hypophysitis. In a study of ipilimumab-induced hypophysitis, 80% had central adrenal insufficiency. Lu et. al. found hypophysitis occurred in 3.25% of patients using ICIs. Of these, it was more common with combination therapy at 7.68% followed by anti-CTLA-4 at 4.53% then anti-PD-1 and anti-PD-L1 at less than 1% of cases (41). Chang et. al. found the combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) caused hypophysitis in 6.4% of patients. Incidence of anti-CTLA-4 alone was 3.2%, anti-PD-1 alone is 0.4%, and anti-PD-L1 alone was 0.1% (42). Overall, the evidence suggests that combination therapy and anti-CTLA-4 have the highest incidence of hypophysitis, while anti-PD-1 and anti-PD-L1 are less common causes of hypophysitis.

PATHOPHYSIOLOGY

The actual pathogenesis is not well defined. Since many patients had no previous immune-related disease before the development of ICI-associated hypophysitis, it was suggested that this condition is not triggered by a pre-existing immune condition. Hypophysitis was initially considered a specific irAE of ipilimumab considering the presence of pituitary expression of CTLA-4 antigens in the TSH, follicle stimulating hormone (FSH), ACTH, and prolactin-secreting cells. Now more recent data suggested that it can occur with any ICI target (CTLA-4, PD-1, or PD-L1) (43, 44). Garon Czmin et. al. reported that the time to develop hypophysitis following initiation of ICIs was significantly shorter with ipilimumab alone or combined with nivolumab (83 days) compared to nivolumab or pembrolizumab alone (165 days). Moreover, ICI-associated hypophysitis is more common in men while autoimmune lymphocytic hypophysitis has a higher prevalence in the female population (43, 45). In one study, hypophysitis with anti-CTLA was four times more common in males compared to females. This may be related to more men having melanoma, but studies controlling for this factor have found similar results (42). Corticotrophs and thyrotrophs are the most common cell types affected while gonadotroph deficiency was more common in male patients. The somatotroph axis and prolactin levels were rarely involved (36).

CLINICAL CHARACTERISTICS

Hypophysitis can occur weeks to months after the initiation of ICIs. In the study by Albarel et. al., mean hypophysitis occurred at 9-9.5 weeks ± 6 weeks after the treatment initiation with a mean age at diagnosis of 55.2 years (36). The initial symptoms are usually related to tumor mass or hormone deficiencies, and rarely visual disturbance or diabetes insipidus. Symptoms may be acute or subacute, but they are usually nonspecific, including headaches, anorexia, dizziness, nausea, weight loss, and/ or fatigue. More serious signs are hypotension, lethargy, confusion, and electrolyte abnormalities including hyponatremia. Hyponatremia occurs due to increased antidiuretic hormone (ADH) stimulated by hypothalamic secretion of CRH. The most common hormone deficiencies include TSH, ACTH, FSH, luteinizing hormone (LH). Panhypopituitarism is less likely to happen. Although hypogonadotropic hypogonadism and central hypothyroidism may resolve, central adrenal insufficiency is permanent requiring lifelong treatment (36, 42). Although, hypo enhancing lesions in the anterior pituitary are characteristic of ICI-associated hypophysitis, a few cases of PD-1/PD-L1 induced-hypophysitis have been reported in the absence of any radiographic abnormalities and just on clinical grounds (46). This suggests that PD-1/PD-L1 may not always show classic pituitary enlargement or enhancement on MRI (47).

SCREENING AND MONITORING

The National Comprehensive Cancer Network (NCCN) guidelines recommend initial serum pituitary hormonal evaluation including morning cortisol, ACTH, TSH, FT3, LH, FSH, testosterone in men, estrogen in premenopausal women, prolactin, growth hormone, and IGF1. The sodium and potassium levels should also be checked. Cosyntropin stimulation test can be normal in acute secondary adrenal insufficiency. Diagnostics radiology reports of brain MRIs in patients receiving ICIs should routinely include comparisons of pituitary size with prior studies. In case of suspected hypophysitis, a dedicated pituitary MRI is recommended. MRI usually showed a pituitary enlargement with or without mass effect however some cases showed pituitary adenoma, empty sella syndrome, or a normal pituitary gland on the imaging studies.

TREATMENT

Once high suspicion for ICI-induced hypophysitis, an endocrinology consult is recommended. High-dose glucocorticoids should be initiated for patients with ipilimumab-induced hypophysitis who have serious mass-effect-related symptoms, such as severe headache, visual-field disturbance, or simultaneously the presence of other irAEs. Patients should be started on methylprednisolone/prednisone at 1-2 mg/kg /day until symptoms resolve, typically 1-2 weeks then taper the steroids rapidly to a physiological dose. In patients without mass effect, studies have suggested that high dose glucocorticoid therapy was not associated with improved outcomes in patients nor change in the natural history of hypophysitis, thus physiological replacement doses can be considered in these patients (28, 36, 48). ICIs should be held until acute symptoms or symptoms related to mass effect have resolved and hormone replacement is initiated (42). One study compared discontinuing ipilimumab to restarting ipilimumab and found no effect on the resolution of hypophysitis (42). In the case of central hypothyroidism, replacement should be started after steroids are initiated. Testosterone and estrogen replacement should be considered in patients with central hypogonadism after discussing the risks and benefits of the medications (28).

Adrenalitis

Primary adrenal insufficiency (PAI), although being a rare endocrine irAEs is a potentially serious condition with significant morbidity and mortality if not identified early. Metastasis to the adrenal gland should be excluded. Other causes of adrenal insufficiency include sudden withdrawal of glucocorticoids and central adrenal insufficiency related to hypophysitis (49).

INCIDENCE

PAI is a rare side effect of ICIs, but early identification is essential given the risk of severe outcomes including death. Early evidence of adrenal insufficiency from ICIs came from case reports, but increasingly more evidence is available from larger studies and meta-analyses (50).
A review and meta-analysis by Barroso-Sousa et. al. that included 62 studies with 5831 patients, found the incidence of PAI was 0.7% for single ICI and 4.2% for combinations of ICIs (8). Another review and meta-analysis by Lu et. al. that included 160 studies and 40,432 patients, examined the rate of pituitary-adrenal dysfunction but did not distinguish the cause of adrenal insufficiency. One complicating factor in the study of PAI is that similar symptoms could occur from hypophysitis or discontinuation of steroids (41). Lu et. al. found adrenal insufficiency occurred in patients on ICIs in 2.43% of cases (ranging from 0-6.4% in studies) with serious grade adrenal effects in 0.15% of cases (ranging from 0-3.3%). Anti-CTLA-4 was associated with higher rates of adrenal insufficiency at 5.32% and serious grade events at 0.42%. Combination therapy also resulted in higher rates of adrenal insufficiency at 4.05%. Anti-PD-1 and anti-PD-L1 accounted for a smaller proportion of events at 0.49% and 0.43% respectively (41).

Grouthier et. al. used the World Health Organization global database, VigiBase, to examine individual safety reports for PAI and ICIs (4). The study found 451 cases of PAI, of which 45 were definite PAI and 406 possible PAI. In the study, 90% of cases involved significant morbidity including prolonged hospitalization, life-threatening illness, and disability. The mortality rate was 7.3%. Importantly the mortality rate appeared to be similar across immunotherapy treatments and combination treatments (4). This suggests that despite a relatively low incidence rate of PAI from ICIs, providers need to be able to identify these cases to prevent the significant risk of morbidity and mortality.

PATHOPHYSIOLOGY

PAI is most frequently caused by autoimmune adrenal insufficiency (AI). Autoimmune AI is seen predominantly in women who make up between 54% to 83% of cases. In contrast, males accounted for the majority of ICI-related PAI cases at 58%, while females accounted for 36% of cases. In the remaining 6%, sex was unspecified. Autoimmune AI generally occurs between 30 to 50 years of age. In contrast, the age of onset with PAI caused by ICIs was 66 years on average with a range of 30-95 years old (1). In autoimmune AI, antibodies to the adrenal cortex including anti-21-hydroxylase are found in 83% to 88% of cases (4). The same antibodies have been found in case reports of ICI-related PAI (42). Adrenal metastasis should be excluded during the workup of adrenal insufficiency.

CLINICAL CHARACTERISTICS

Symptoms of PAI related to ICIs are similar to PAI from other causes. Symptoms include fatigue, postural dizziness, orthostatic hypotension, anorexia, weight loss, and abdominal pain. Adrenal crisis is suggested by altered mental status, weakness, syncope, nausea, and vomiting (42). In 52% of cases, other irAEs were also present. Other endocrinopathies made up 14.9% of these irAEs. The median time to onset was 120 days (ranging from 6-576 days) from starting the ICIs (4). Lab findings include hyponatremia, hyperkalemia, hypoglycemia, hypercalcemia, low aldosterone, elevated renin, elevated ACTH, and low to low normal cortisol. Imaging may reveal adrenalitis with enlarged adrenal glands. Interestingly, one case report found imaging evidence of adrenalitis present on a positron emission tomography (PET) scan after starting ipilimumab, but no symptoms or biochemical evidence of adrenal insufficiency. Repeat imaging revealed normal adrenal glands months later. This case suggests adrenalitis may occur without adrenal insufficiency (42).

SCREENING AND MONITORING

The NCCN guidelines recommend checking morning cortisol before each treatment or every four weeks during treatment. Additionally, follow-up testing is recommended for an additional six to twelve weeks. If cortisol is low or subnormal, ACTH monitoring is recommended. To monitor for pituitary and thyroid dysfunction, TSH and T4 monitoring at similar intervals are also recommended (28). In a review by Chang et. al., monitoring was recommended only in symptomatic patients, but a low index for suspicion was recommended as symptoms are nonspecific. When a patient has suspicious symptoms for adrenal dysfunction, ACTH and cortisol should be obtained before corticosteroid treatment only if this can be done safely. Additionally, measuring renin and aldosterone is helpful to determine if mineralocorticoid deficiency is present. This can be particularly helpful as case reports of central and PAI coexisting have been reported. The utility of adrenal autoantibodies, including 21-hydroxylase, is not well-established (42).

TREATMENT

PAI caused by ICIs is treated the same as other causes of PAI. If adrenal crisis or other critical illness is present, stress dose steroids with 100mg IV then 50mg IV every six hours is initiated. In stable patients,

15-25mg hydrocortisone is started in divided doses. Fludrocortisone is used to treat mineralocorticoid deficiency in PAI starting at 0.5-1mg daily. Additionally, patients will need to be educated on sick day rules and be provided with medical alert bracelets, and have high-dose corticosteroids for emergency purposes (28). The other important aspect of treatment is the decision to continue the ICIs. Holding the ICIs is recommended upon identification of adrenal insufficiency. Restarting immunotherapy can be considered after stabilization on hydrocortisone and fludrocortisone replacement.

Type 1 Diabetes

Rapid onset of autoimmune diabetes has been reported with ICIs use. It is a rare but life-threatening side effect as it can present with diabetic ketoacidosis (DKA). The diabetes is permanent and requires lifelong treatment with insulin therapy (51). Notably, ICI-induced type 1 diabetes (T1D) has been reported with all clinically available PD-1 (nivolumab, pembrolizumab) and PD-L1 inhibitors (avelumab, durvalumab, atezolizumab) but rarely with the CTLA-4 inhibitor (ipilimumab).

INCIDENCE

The incidence of ICI-induced T1D comes from large case series at academic medical centers reporting 27 cases out of 2960 patients receiving ICI therapy (0.9%) (52) and 1/1163 (1.8%) (53). Additionally, the prescription label for nivolumab reports that 17/1994 (0.9%) cases developed T1D (54). However, when examining the clinical trials evaluating the efficacy of PD-1 and PD-L1 inhibitors, there is a wide range of reported hyperglycemia and diabetes (55-64) (Table 1). From this analysis, hyperglycemia or diabetes was reported in approximately 2.5% of treated individuals.

Table 1. Clinical Trials Reporting Hyperglycemia/Diabetes with ICIs Use

Authors, Journal and Publication Year	Cases (n)	Study Participants (n)	Side effect (%)	Side effect	Drug	Cancer Type
Hamid et. al. NEJM, 2013 (55)	4	135	2.96	Hyperglycemia	Lambrolizumab	Melanoma
Borghaei et. al. NEJM, 2015 (56)	13	287	4.52	Hyperglycemia	Nivolumab	Lung
Motzer et. al. NEJM, 2015 (57)	9	406	2.21	Hyperglycemia	Nivolumab	Renal cell
Robert et. al. NEJM, 2016 (58)	1	206	0.48	Diabetes	Nivolumab	Melanoma
Nghiem et. al. NEJM, 2016 (59)	1	26	3.84	Hyperglycemia	Pembrolizumab	Merkel-cell
Kaufman et. al. Lancet, 2016 (60)	1	88	1.13	Type 1 Diabetes	Avelumab	Merkel-cell
Reck et. al. NEJM, 2016 (61)	1	154	0.64	Type 1 Diabetes	Pembrolizumab	Lung
Heery et. al. Lancet, 2017 (62)	3	53	5.66	Hyperglycemia	Avelumab	Solid tumors
Weber et. al. NEJM, 2017 (63)	2	452	0.44	Diabetes	Nivolumab	Melanoma

Choueiri et. al. Lancet, 2018 (64)	7	55	12.7	Hyperglycemia	Avelumab	Renal cell

Of note, most of the clinical trials in Table 1 excluded patients with a preexisting autoimmune condition, and some even excluded patients with a family history of autoimmunity. As these therapies are now being more widely used in clinical practice, there is an increased reporting of ICIs-induced diabetes (65). This is likely due to the increasing use of ICIs therapy and differences in patient populations between phase 2/3 clinical trials and clinical practice. Although T1D is a relatively rare occurrence with ICIs therapy, the events are clinically significant.

PATHOPHYSIOLOGY

The first case series reporting ICIs-induced autoimmune diabetes was described in 2015 (66). In this series of five patients, both humoral and cellular diabetes-associated autoimmunity were described. Some patients had positive T1D associated autoantibodies and diabetes-specific CD8+ T cells in the peripheral blood, consistent with findings from childhood-onset T1D (66).

The role of the PD-1/PD-L1 pathway in preclinical animal models of T1D has been appreciated for over a decade. Non-obese-diabetic (NOD) mice develop spontaneous autoimmune diabetes so it has been used extensively as an animal model to understand the mechanisms of T1D development (67). NOD mice with a knockout of either PD-1 or PD-L1 (but not PD-L2) have accelerated onset of diabetes with lymphocytic infiltration of the pancreatic islets (e.g., insulitis) compared to mice with these immune regulatory molecules (68, 69). Furthermore, administration of anti-PD-1 or PD-L1 monoclonal antibodies to NOD mice also accelerated the onset of T1D (70). When examining the islets in NOD mice, insulin-producing beta-cells express PD-L1 during the progression of autoimmune diabetes (71). Similar to NOD mice, human islets from T1D organ donors exhibit upregulation of PD-L1, which was strongly associated with insulitis (72). This likely represents a protective mechanism for beta-cells to lessen their autoimmune destruction. These studies may explain why anti-PD-1/PD-L1 therapies induce T1D, while there is an absence of diabetes with anti-CTLA-4 therapy, whose ligands are CD80 and CD86 on antigen-presenting cells such as B cells, dendritic cells, and macrophages.

CLINICAL CHARACTERISTICS

Over the last 4 years, cases have described rapid-onset insulin-dependent diabetes with undetectable C-peptide levels (a measure of residual beta-cell function) and both positive and negative T1D associated autoantibodies at presentation (73, 74). Cases of ICIs-induced T1D have remained insulin-dependent even upon stopping therapy. Steroid treatment has not been able to reverse T1D, and as expected, blood glucose worsens with steroid administration (75, 76).

ICIs-induced T1D is mostly reported in older patients (50-70 years old) due to the nature of end-stage cancers developing later in life. More cases have been reported with anti-PD-1 therapies (nivolumab and pembrolizumab) as these agents were approved before monoclonal antibodies targeting anti-PD-L1 (51, 66, 73, 74, 77). Melanoma is the most common cancer in patients that present with ICIs-induced T1D, likely due to this being the first approved indication for ICIs therapy, and more patients with melanoma have been exposed to ICIs therapy compared to other cancer types. However, with the expanding indications and recent approval of ICIs therapy for use in pediatric cancers, ICIs-induced T1D may increase and present in younger individuals (78).

METABOLIC FEATURES

ICIs-induced T1D presents within days to a year after the initiation of PD-1 or PD-L1 therapy. HbA1c, which

is a measure of the average blood glucose over the preceding three months, is generally lower than 10% at presentation with most patients presenting between 7 to 8%. As these values are mildly elevated, this suggests significant hyperglycemia over a short period rather than a gradual increase in hyperglycemia over a longer period. Most of the patients present with severe DKA that can be life-threatening. In most cases, C-peptide levels were inappropriately low for the presenting blood glucose or undetectable; 'honeymoon' periods tend to be absent after diagnosis. These observations suggest a destruction of beta-cell mass. In some patients, increased amylase and/or lipase has been reported, suggesting more generalized pancreatic inflammation (52, 79).

IMMUNOLOGIC FEATURES

At least one T1D associated autoantibody, directed against insulin, glutamic acid decarboxylase (GAD), islet antigen-2 (IA-2), and zinc transporter 8 (ZnT8), was reported in 40-50% of the cases (52, 79). Almost all antibody-positive cases had GADA antibodies; however, not all four major autoantibodies were reported or measured in these case series. It is speculated that there is an association between antibody presence and earlier onset of ICIs-induced T1D in a subset of patients. In one case, positive conversion of antibodies after ICIs therapy was reported (52). Polyclonal and predominantly IgG_1 subclass for GADA was shown at the presentation of another case that developed T1D five days after the initiation of PD-1 inhibitor therapy. Since IgG antibodies are involved in memory immune response and the short time interval from the initiation of anti-PD-1 treatment to the onset of T1D, these antibodies were likely present before the start of therapy (51). Based on these findings, a subset of patients developing ICIs-induced T1D likely have preexisting T1D associated antibodies which may be an early form of latent autoimmune diabetes of adulthood (LADA); however, prospective studies measuring T1D associated antibodies before the start of ICIs therapy are needed to evaluate this hypothesis.

GENETIC RISKS

Human leukocyte antigen (HLA) genes on chromosome 6 confer genetic risk for many autoimmune disorders including childhood-onset T1D (80). The polymorphic class II HLA genes (DQ, DR, and DP) confer this risk, especially the DR4-DQ8 and DR3-DQ2 haplotypes (81, 82). Only a small number of cases with ICIs-induced T1D have reported HLA genes with some having T1D risk alleles. In one case series, the frequency of HLA-DR4 was found to be enriched in those with ICIs-induced T1D compared to rates among Caucasians in the US population (52, 79). Further research is necessary to identify HLA and other genetic variants that may confer risk for ICIs-induced T1D.

COMPARISON TO CHILDHOOD-ONSET TYPE 1 DIABETES

We believe it is useful to compare the current knowledge of ICIs-induced T1D to prototypical childhood-onset T1D (Table 2). The age of onset is distinctly different between the two types of diabetes. Presentation with DKA is more common and the onset of diabetes more rapid than traditional T1D. T1D associated autoantibodies are present in ~90% of children and adolescents with T1D compared to half of the reported cases in ICIs-induced T1D. There is a predominance of GAD autoantibodies at the presentation of ICIs-induced T1D; however, more research is needed to measure all four major T1D associated autoantibodies in these patients and those directed against post-translationally modified antigens may also reveal insights into the pathogenesis of the disorder. C-peptide levels are low or undetected in those treated with ICIs therapy that develops T1D compared to C-peptide levels that vary and gradually go down after the diagnosis of childhood T1D. As a corollary, the honeymoon phase is generally absent in ICIs-induced T1D (80-83).

Table 2. Comparison Between Prototypical and Immune Checkpoint Inhibitor-Induced Type 1 Diabetes		
Characteristics	**Prototypical Type 1 Diabetes**	**Immune Checkpoint Inhibitor-Induced Type 1 Diabetes**
Age of Onset	Peak in early childhood & adolescence	Later adulthood, 60's
Diabetic ketoacidosis at Onset	Common	Very common
Pathophysiology	Autoimmune (years)	Autoimmune (days to months)
Autoantibodies	Present in 90-95%	Present in ~50%*
HLA Risk Genes	~90%	75-80%+
C-peptide at presentation	Varies	Low/absent
Honeymoon phase	Present	Absent

*Predominantly GADA antibodies;
+Small sample size, as not all cases report HLA alleles; there is an association with HLA-DR4

SCREENING AND MONITORING

The most updated recommendation on screening for diabetes in patient receiving ICIss comes from 2018 American Society of Clinical Oncology (ASCO) clinical practice guidelines, which recommends monitoring blood glucose at baseline, with each treatment cycle for 12 weeks and then every 3-6 weeks thereafter (24). In cases with suspected T1DM such as new onset hyperglycemia >200 mg/dl, random blood sugar >250 or history of T2DM with glucose levels >250 mg/dl, further testing for ketosis and anion gap is recommended (24). Discussing the risk of developing T1D with patients and educating them about the signs and symptoms of diabetes and DKA are recommended. Based on the current evidence, patients who have positive T1D associated antibodies and certain HLA alleles may have an increased risk to develop diabetes, so screening antibodies and reporting HLA alleles before the initiation of treatment may identify these patients with greater risk.

A retrospective study evaluated fasting blood glucose levels of patients receiving ICIs treatment during patient visits and showed no detectable upward drift of glycemia before DKA presentation (83). This is likely due to the rapid onset and progression of ICI-induced T1D. However, we believe monitoring blood glucose and HbA1c levels during patient visits are still necessary. Considering the rapid onset of diabetes, this approach alone may miss a significant amount of hyperglycemia and DKA. We recommend routine self-monitoring of blood glucose by patients and/or using continuous glucose monitoring to recognize hyperglycemia before DKA presentation. Close monitoring of patients with preexisting autoimmunity may also be useful (51). Our suggested screening and monitoring algorithm is depicted in Figure 3.

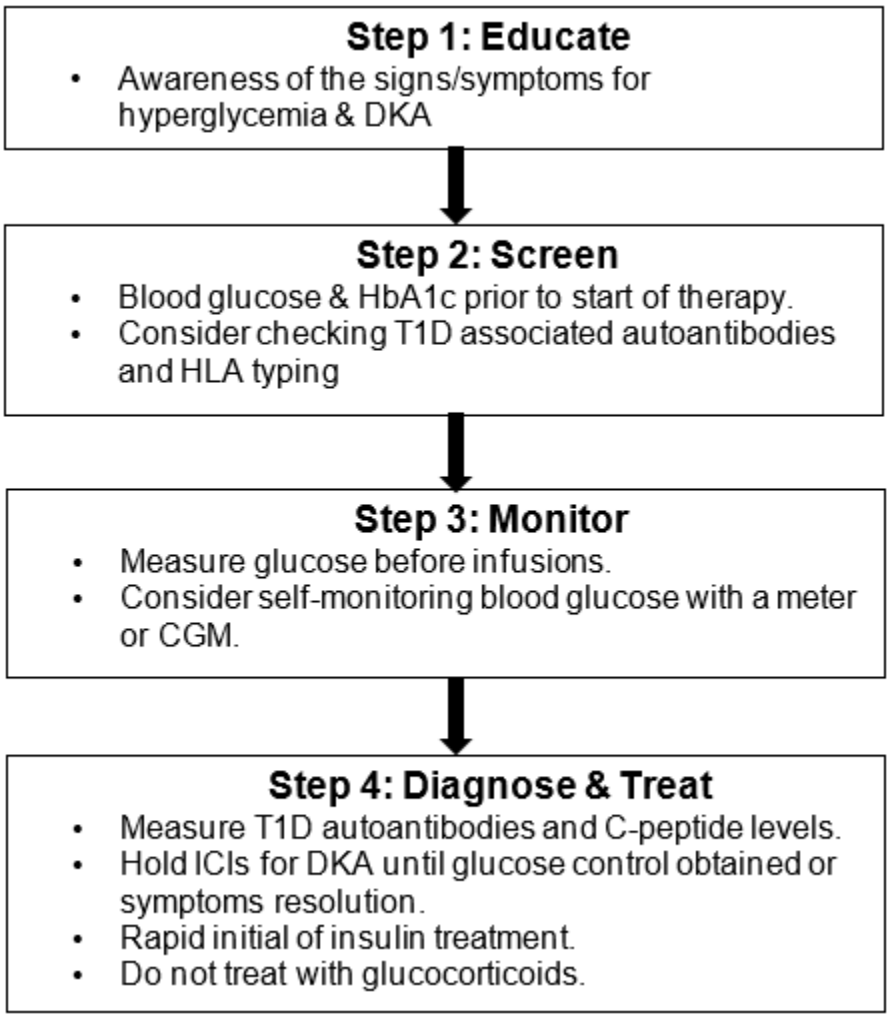

Figure 3. Proposed algorithm to screen and manage patients for ICI-induced T1D. (DKA = diabetic ketoacidosis; HbA1c = Hemoglobin A1c, T1D= Type 1 diabetes, HLA = human leukocyte antigen, CGM = continuous glucose monitor)

Hypogonadism

The effects of ICIs on sexual function are not very well known. ICI-induced primary hypogonadism is rare but a life-changing side effect, as it can potentially lead to infertility. Notably, gonadal dysfunction has been reported for ipilimumab monotherapy or in combination with PD-1/PD-L1 inhibitors (84). The long-term effects are still largely unknown. ICI-induced male hypogonadism is characterized by a deficiency in testosterone, which can be due to testicular, hypothalamic, or pituitary abnormalities. ICI-associated hypophysitis is discussed separately, and this section will primarily focus on ICI-induced primary hypogonadism.

INCIDENCE

Although, ICI-associated hypogonadism can be seen in patients who develop panhypopituitarism secondary to ICI-associated hypophysitis, the true occurrence of primary hypogonadism is uncommon and is based on a few case reports and ongoing studies (84-86). A recent analysis of VigiBase, the WHO global database of individual case safety reports between 2011 and 2019, found only 1 case of primary hypogonadism

(87). This surprisingly low incidence may in fact be due to lack of proper evaluation looking for primary hypogonadism. For example, many studies reporting occurrence of secondary hypogonadism lacked data on the levels of pituitary gonadotropins, FSH and LH, which is necessary to differentiate between primary and secondary hypogonadism (43). Moreover, the majority of the pivotal trials leading to FDA approval of ICIs lacked information regarding fertility, menopause status, sex hormone levels, or sexual health-related quality of life. Additionally, not much is known about ICI-associated infertility. In a study of patients with malignant melanoma treated with ICIs, 6 of 7 men (86%) with testicular autopsy tissue samples had impaired spermatogenesis (88). This may suggest higher prevalence of infertility among men receiving ICIs. No data on potential effects on female fertility are currently available.

PATHOPHYSIOLOGY

ICIs may cause irAEs affecting any organ in the body by blocking regulators of self-tolerance. The understanding of pathophysiologic mechanism of ICI-induced primary hypogonadism comes from limited number of cases reports (85, 86). In the first case, the patient developed bilateral orchitis two weeks following administration of nivolumab and laboratory workup confirmed diagnosis of primary hypogonadism (decreased testosterone with elevated LH) (85). However, it self-resolved within one week without use of steroids or any other therapy, and there was no recurrence. The intensity and timing of the orchitis suggests an intense immune stimulation leading to orchitis and primary hypogonadism (85). In another case, the patient developed bilateral epididymo-orchitis following administration of the third dose of pembrolizumab and needed high-dose steroids resulting in complete resolution (86). The testis is considered an immune-privileged organ due to its ability to tolerate autoantigens. The use of experimental autoimmune orchitis (EAO) in rats has allowed analysis of the autoimmune inflammatory response to spermatic antigens, providing a steppingstone towards understanding the ICI-induced primary hypogonadism. The main mechanisms responsible for preventing autoimmune disease of testes are: (a) secretion of immunosuppressive factors by macrophages, Sertoli cells, and Leydig cells, (b) presence of blood-testis barrier (BTB), and (c) presence of regulatory T cells. There is a fine equilibrium between dendritic cells, macrophages, T cells, and cytokines in maintaining immunosuppression in testes. While there have been no studies to date specifically evaluating the mechanism of ICI-induced orchitis, the examination of the normal and altered autoimmune immunobiology elucidates the possible mechanisms involved (89). This is briefly described below:

Secretion of Immunosuppressive Factors

In the normal testis macrophages, Sertoli and Leydig cells create an immunosuppressor microenvironment by secreting factors and cytokines that inhibit immune reactions. These include transforming growth factor-beta, granulocyte-macrophage colony stimulating factor, alpha-endorphin, and insulin-growth factor-1 (89, 90). In the setting of EAO, there is increased recruitment and activation of immune cells to the interstitium which bring along with them secretion of pro-inflammatory cytokines (IL-6, IFN-gamma, TNF-alpha, IL-17, IL-23). This brings about a cascade of events leading to germ cell apoptosis, primarily via the section of TNF-alpha (89, 91)

Blood-Testis Barrier (BTB)

In the normal testis, the BTB limits the interaction between germ cell antigens and interstitial immune cells. Secretion of pro-inflammatory cytokines mentioned above act on adherens and tight junctions, altering the BTB permeability (92). After crossing the BTB, these cytokines enter the seminiferous tubules inducing apoptosis of germ cells and facilitating the release of spermatic antigens, which then go on to interact with interstitial immune cells (92).

Presence of Regulatory T Cells (Tregs)

In the normal testis, there are several subsets of T cells present, regulating immune responses. Tregs specifically, mediate tolerance to self-antigens and their suppression sets the stage for autoimmunity. While there are increased Tregs seen in chronic inflamed testis, these are overwhelmed by the inhibitory effects of effector T cells, affecting the ability of Tregs to control autoimmunity (93). CTLA-4 inhibits effector T cells and PD-1/PDL-1 binding promotes the conversion of Teff to Treg. Therefore, it is plausible that the use of the combination of ipilimumab with an anti-PD-1/PDL-1 antibody, tips the balance between Tregs and effector cells toward the effector T cells. Consequently, creating a pro-inflammatory state resulting in orchitis.

LONG-TERM OUTCOMES AND TREATMENT

It is well established that inflammation and infection of the male reproductive tract may lead to infertility in males (94). Therefore, it is reasonable to postulate that ICI-induced orchitis may also lead to male infertility, a consequence that should be addressed by providers. The long-term outcomes of ICIs are just beginning to be explored. One retrospective review assessed patients who became infertile after ICI therapy and subsequently died. Retrospective cohort cadaver study analyzing tissue specimens of the testes showed 86% of men who received ICI therapy had impaired spermatogenesis (88). Notably, there was no increased peritubular hyalinization or fibrosis in the treated group, and no changes in Leydig cells (88). These findings support the previously mentioned pathophysiology of ICI-induced orchitis and address the possibility of infertility as a long-term consequence. Given the limited information on the effects of ICIs in spermatogenesis, providers should provide patients with their options, such as sperm banking and cryopreservation (95).

Other Uncommon Endocrine Side Effects

ACQUIRED GENERALIZED LIPODYSTROPHY

Lipodystrophy is characterized by absent of visceral or subcutaneous adipose tissue in the settings of normal non-starvation nutritional state. It is a known common side effect from certain medications such as older HIV protease inhibitor, which is a reversible side effect. While the mechanism of lipodystrophy from ICIs is currently unclear, it is believed that the medication may induced an autoimmune process that leads to fat destruction by forming anti-adipocyte antibodies. In ICI-induced lipodystrophy, the more common form appears to be acquired generalized lipodystrophy (AGL) in which all fat tissues are affected but may spare the neck and face region. Onset of AGL, can be as early as 2-4 months which is roughly after 4-5 doses of ICIs. Currently, most of the cases of ICI-induced AGL are associated with nivolumab therapy (96, 97).

HYPOPARATHYROIDISM AND HYPOCALCEMIA

Another rare but crucial endocrine irAEs is hypocalcemia secondary to hypoparathyroidism. While the exact mechanism is unclear, the proposed etiology is due to calcium-sensing receptor (CaSR) activating autoantibodies. This antibody is also present in patients with autoimmune polyendocrine syndrome type 1 (APS1) or idiopathic hypoparathyroidism. The clinical presentation can be as abrupt as an acute symptomatic hypocalcemia episode which includes paresthesia, tetany, and potential arrhythmias requiring hospitalization but may also present as very mild to asymptomatic hypocalcemia. For both circumstances, calcium and vitamin D replacement are adequate therapy but patients should be closely monitored for severe symptoms (98).

CENTRAL DIABETES INSIPIDUS

Posterior pituitary hormone secretion can also be affected with ICIs, mainly antidiuretic hormones

(ADH), which can subsequently lead to sodium and water dysregulation. To our knowledge only 3 cases of central diabetes insipidus (CDI) has been reported with the use of nivolumab (PD-1 inhibitor) and Azelumab (PD-L1 inhibitor) (99-101).The patients presented with classic polyuria/polydipsia symptoms along with hypernatremia which responded well to desmopressin (99-101). In the case report described by Fosci et. al., the authors described coexistence of metastatic localization and infundibulo-neurohypophysitis on MRI (100) while in the case report by Deligiori et. al., there was no signs of hypophysitis on imaging (99). Thus, further investigation is needed to fully understand the possible mechanisms for CDI.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

SIADH is the opposite scenario in which patients present with euvolemic hyponatremia. It is somewhat difficult to distinguish for certain that SIADH is truly from ICIs since SIADH is quite common in patients with underlying malignancies. Additionally, pain in patients with cancer itself can be the underlying cause of SIADH. Additionally, there are some reports of hyponatremia as a manifestation of adrenal insufficiency in patients on ICIs and hence it is crucial to rule out adrenal insufficiency for any patient with hyponatremia, as immediate recognition and treatment can be lifesaving (102, 103).

VITILIGO

Depigmentation of skin or vitiligo is thought to be from inducing an immune response to normal melanocyte antigens leading to the destructive process. While vitiligo itself may not be directly endocrine-related, its presence has been strongly associated with common endocrinopathies such as thyroid and adrenal disease as well as autoimmune diabetes. Interestingly, when vitiligo is present as one of the side effects from ICIs, this may represent a better prognosis in melanoma cases (104).

Figure 4. Proposed algorithm to screen and manage patients with endocrine irAEs

Table 3. Summary of the Common Terminology Criteria for Adverse Events (28)		
Grade	**Severity of Adverse events**	**Management**
1	Mild (asymptomatic or mild symptoms)	Clinical or diagnostic observation
2	Moderate	Minimal, local or noninvasive intervention indicated
3	Severe or medically significant but not immediate life threatening	Intervention is required
4	Life threatening	Urgent intervention indication
5	Death	

Table 4. Summary of the Incidence of Endocrine iRAEs (8,16,23, 41, 55-64, 105)			
irAEs	**PD-1/L1 inhibitors**	**CTLA-4 inhibitors**	**Combination**
Hypophysitis	Less than 1 %	0-17%	More common than single drug use.
Hypothyroidism	7-21%	0-6%	
hyperthyroidism	Higher in PD1 inhibitors compared to PDL1 inhibitors	Less common than PD-1/PDL1 inhibitors	
Primary adrenal insufficiency	Less common than CTLA-4 inhibitors	More common than PD-1/PDL1 inhibitors	
Diabetes	Around 2.5%	None reported	

CONCLUSION

Considering the increasing use of immune checkpoint inhibitors in clinical practice, health care providers and patients should be aware of endocrine irAEs. Educating patients receiving and providers using these state-of-the-art therapies about the signs and symptoms of different endocrinopathies is critical for an early diagnosis to prevent life-threatening complications. Developing screening and monitoring guidelines are essential to identify at-risk patients for close monitoring of these unwanted side effect.

REFERENCES

1. Thangamathesvaran L, Shah R, Verma R, Mahmoud O. Immune checkpoint inhibitors and radiotherapy-concept and review of current literature. Ann Transl Med. 2018;6(8):155.
2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-64.
3. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science. 1996;271(5256):1734-6.
4. Grouthier V, Lebrun-Vignes B, Moey M, Johnson DB, Moslehi JJ, Salem JE, et al. Immune Checkpoint Inhibitor-Associated Primary Adrenal Insufficiency: WHO VigiBase Report Analysis. Oncologist. 2020;25(8):696-701.
5. Peggs KS, Quezada SA, Korman AJ, Allison JP. Principles and use of anti-CTLA4 antibody in human cancer immunotherapy. Curr Opin Immunol. 2006;18(2):206-13.
6. Thompson RH, Dong H, Kwon ED. Implications of B7-H1 expression in clear cell carcinoma of the kidney for prognostication and therapy. Clin Cancer Res. 2007;13(2 Pt 2):709s-15s.
7. Zang X, Allison JP. The B7 family and cancer therapy: costimulation and coinhibition. Clin Cancer Res. 2007;13(18 Pt 1):5271-9.
8. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, 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.
9. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and

associated endocrinopathies. Nat Rev Endocrinol. 2017;13(4):195-207.
10. Weber JS, Dummer R, de Pril V, Lebbé C, Hodi FS. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer. 2013;119(9):1675-82.
11. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. JAMA Oncol. 2016;2(2):234-40.
12. Eggermont AMM, Kicinski M, Blank CU, Mandala M, Long GV, Atkinson V, et al. Association Between Immune-Related Adverse Events and Recurrence-Free Survival Among Patients With Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo: A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol. 2020;6(4):519-27.
13. Maher VE, Fernandes LL, Weinstock C, Tang S, Agarwal S, Brave M, et al. Analysis of the Association Between Adverse Events and Outcome in Patients Receiving a Programmed Death Protein 1 or Programmed Death Ligand 1 Antibody. J Clin Oncol. 2019;37(30):2730-7.
14. Suo A, Chan Y, Beaulieu C, Kong S, Cheung WY, Monzon JG, et al. Anti-PD1-Induced Immune-Related Adverse Events and Survival Outcomes in Advanced Melanoma. Oncologist. 2020;25(5):438-46.
15. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of endocrine complications in cancer patients treated with immune check point inhibitors: a meta-analysis. Future Oncol. 2016;12(3):413-25.
16. Kotwal A, Kottschade L, Ryder M. PD-L1 Inhibitor-Induced Thyroiditis Is Associated with Better Overall Survival in Cancer Patients. Thyroid. 2020;30(2):177-84.
17. Delivanis DA, Gustafson MP, Bornschlegl S, Merten MM, Kottschade L, Withers S, et al. Pembrolizumab-Induced Thyroiditis: Comprehensive Clinical Review and Insights Into Underlying Involved Mechanisms. The Journal of clinical endocrinology and metabolism. 2017;102(8):2770-80.
18. Kobayashi T, Iwama S, Yasuda Y, Okada N, Tsunekawa T, Onoue T, et al. Patients With Antithyroid Antibodies Are Prone To Develop Destructive Thyroiditis by Nivolumab: A Prospective Study. J Endocr Soc. 2018;2(3):241-51.
19. Toi Y, Sugawara S, Sugisaka J, Ono H, Kawashima Y, Aiba T, et al. Profiling Preexisting Antibodies in Patients Treated With Anti-PD-1 Therapy for Advanced Non-Small Cell Lung Cancer. JAMA Oncol. 2019;5(3):376-83.
20. Kurimoto C, Inaba H, Ariyasu H, Iwakura H, Ueda Y, Uraki S, et al. Predictive and sensitive biomarkers for thyroid dysfunctions during treatment with immune-checkpoint inhibitors. Cancer Sci. 2020;111(5):1468-77.
21. Angell TE, Min L, Wieczorek TJ, Hodi FS. Unique Cytologic Features of Thyroiditis Caused by Immune Checkpoint Inhibitor Therapy for Malignant Melanoma. Genes Dis. 2018;5(1):46-8.
22. Tan MH, Iyengar R, Mizokami-Stout K, Yentz S, MacEachern MP, Shen LY, et al. Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients: a scoping review of case reports. Clin Diabetes Endocrinol. 2019;5:1.
23. Wright JJ, Powers AC, Johnson DB. Endocrine toxicities of immune checkpoint inhibitors. Nat Rev Endocrinol. 2021;17(7):389-99.
24. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68.
25. Network NCC. Management of Immunotherapy-Related Toxicities Version 4.2021 2021 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.
26. Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. Bmj. 2019;365:l2006.
27. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J. 2013;2(4):215-28.
28. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. Management of Immunotherapy-Related Toxicities, Version 1.2019. J Natl Compr Canc Netw. 2019;17(3):255-89.
29. Brancatella A, Viola N, Brogioni S, Montanelli L, Sardella C, Vitti P, et al. Graves' Disease Induced by Immune Checkpoint Inhibitors: A Case Report and Review of the Literature. Eur Thyroid J. 2019;8(4):192-5.
30. Iyer PC, Cabanillas ME, Waguespack SG, Hu MI, Thosani S, Lavis VR, et al. Immune-Related Thyroiditis with Immune Checkpoint Inhibitors. Thyroid. 2018;28(10):1243-51.
31. Yamauchi I, Sakane Y, Fukuda Y, Fujii T, Taura D, Hirata M, et al. Clinical Features of Nivolumab-Induced Thyroiditis: A Case Series Study. Thyroid. 2017;27(7):894-901.
32. Yonezaki K, Kobayashi T, Imachi H, Yoshimoto T, Kikuchi F, Fukunaga K, et al. Combination therapy of ipilimumab and nivolumab induced thyroid storm in a patient with Hashimoto's disease and diabetes mellitus: a case report. Journal of medical case reports. 2018;12(1):171.
33. Yu C, Chopra IJ, Ha E. A novel melanoma therapy stirs up a storm: ipilimumab-induced thyrotoxicosis.

Endocrinol Diabetes Metab Case Rep. 2015;2015:140092.
34. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343-421.
35. Sjolin G, Holmberg M, Torring O, Bystrom K, Khamisi S, de Laval D, et al. The Long-Term Outcome of Treatment for Graves' Hyperthyroidism. Thyroid. 2019;29(11):1545-57.
36. Albarel F, Gaudy C, Castinetti F, Carre T, Morange I, Conte-Devolx B, et al. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol. 2015;172(2):195-204.
37. Faje AT, Sullivan R, Lawrence D, Tritos NA, Fadden R, Klibanski A, et al. Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. The Journal of clinical endocrinology and metabolism. 2014;99(11):4078-85.
38. Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. Endocr Rev. 2005;26(5):599-614.
39. González-Rodríguez E, Rodríguez-Abreu D. Immune Checkpoint Inhibitors: Review and Management of Endocrine Adverse Events. Oncologist. 2016;21(7):804-16.
40. Torino F, Barnabei A, Paragliola RM, Marchetti P, Salvatori R, Corsello SM. Endocrine side-effects of anti-cancer drugs: mAbs and pituitary dysfunction: clinical evidence and pathogenic hypotheses. Eur J Endocrinol. 2013;169(6):R153-64.
41. Lu J, Li L, Lan Y, Liang Y, Meng H. Immune checkpoint inhibitor-associated pituitary-adrenal dysfunction: A systematic review and meta-analysis. Cancer Med. 2019;8(18):7503-15.
42. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. Endocr Rev. 2019;40(1):17-65.
43. Garon-Czmil J, Petitpain N, Rouby F, Sassier M, Babai S, Yéléhé-Okouma M, et al. Immune check point inhibitors-induced hypophysitis: a retrospective analysis of the French Pharmacovigilance database. Scientific reports. 2019;9(1):19419.
44. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med. 2014;6(230):230ra45.
45. Falorni A, Minarelli V, Bartoloni E, Alunno A, Gerli R. Diagnosis and classification of autoimmune hypophysitis. Autoimmun Rev. 2014;13(4-5):412-6.
46. Kurokawa R, Ota Y, Gonoi W, Hagiwara A, Kurokawa M, Mori H, et al. MRI Findings of Immune Checkpoint Inhibitor-Induced Hypophysitis: Possible Association with Fibrosis. AJNR Am J Neuroradiol. 2020;41(9):1683-9.
47. Lupi I, Brancatella A, Cosottini M, Viola N, Lanzolla G, Sgrò D, et al. Clinical heterogeneity of hypophysitis secondary to PD-1/PD-L1 blockade: insights from four cases. Endocrinol Diabetes Metab Case Rep. 2019;2019.
48. Blansfield JA, Beck KE, Tran K, Yang JC, Hughes MS, Kammula US, et al. Cytotoxic T-lymphocyte-associated antigen-4 blockage can induce autoimmune hypophysitis in patients with metastatic melanoma and renal cancer. J Immunother. 2005;28(6):593-8.
49. Haissaguerre M, Hescot S, Bertherat J, Chabre O. Expert opinions on adrenal complications in immunotherapy. Ann Endocrinol (Paris). 2018;79(5):539-44.
50. Elshimy G, Gandhi A, Guo R, Correa R. Tyrosine Kinase Inhibitors' Newly Reported Endocrine Side Effect: Pazopanib-Induced Primary Adrenal Insufficiency in a Patient With Metastatic Renal Cell Cancer. J Investig Med High Impact Case Rep. 2020;8:2324709620936808.
51. Akturk HK, Alkanani A, Zhao Z, Yu L, Michels AW. PD-1 Inhibitor Immune-Related Adverse Events in Patients With Preexisting Endocrine Autoimmunity. The Journal of clinical endocrinology and metabolism. 2018;103(10):3589-92.
52. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, et al. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. Diabetes. 2018;67(8):1471-80.
53. Kotwal A, Haddox C, Block M, Kudva YC. Immune checkpoint inhibitors: an emerging cause of insulin-dependent diabetes. BMJ Open Diabetes Res Care. 2019;7(1):e000591.
54. Nivolumab label information 2018 [Available from: https://packageinserts.bms.com/pi/pi_opdivo.pdf.
55. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. The New England journal of medicine. 2013;369(2):134-44.
56. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. The New England journal of medicine. 2015;373(17):1627-39.
57. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. The New England journal of medicine. 2015;373(19):1803-13.

58. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. The New England journal of medicine. 2015;372(4):320-30.
59. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. The New England journal of medicine. 2016;374(26):2542-52.
60. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016;17(10):1374-85.
61. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine. 2016;375(19):1823-33.
62. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol. 2017;18(5):587-98.
63. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. The New England journal of medicine. 2017;377(19):1824-35.
64. Choueiri TK, Larkin J, Oya M, Thistlethwaite F, Martignoni M, Nathan P, et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. Lancet Oncol. 2018;19(4):451-60.
65. Wright JJ, Salem JE, Johnson DB, Lebrun-Vignes B, Stamatouli A, Thomas JW, et al. Increased Reporting of Immune Checkpoint Inhibitor-Associated Diabetes. Diabetes care. 2018;41(12):e150-e1.
66. Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, et al. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care. 2015;38(4):e55-7.
67. Mullen Y. Development of the Nonobese Diabetic Mouse and Contribution of Animal Models for Understanding Type 1 Diabetes. Pancreas. 2017;46(4):455-66.
68. Wang J, Yoshida T, Nakaki F, Hiai H, Okazaki T, Honjo T. Establishment of NOD-Pdcd1-/- mice as an efficient animal model of type I diabetes. Proc Natl Acad Sci U S A. 2005;102(33):11823-8.
69. Keir ME, Liang SC, Guleria I, Latchman YE, Qipo A, Albacker LA, et al. Tissue expression of PD-L1 mediates peripheral T cell tolerance. J Exp Med. 2006;203(4):883-95.
70. Ansari MJ, Salama AD, Chitnis T, Smith RN, Yagita H, Akiba H, et al. The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. J Exp Med. 2003;198(1):63-9.
71. Rui J, Deng S, Arazi A, Perdigoto AL, Liu Z, Herold KC. beta Cells that Resist Immunological Attack Develop during Progression of Autoimmune Diabetes in NOD Mice. Cell metabolism. 2017;25(3):727-38.
72. Osum KC, Burrack AL, Martinov T, Sahli NL, Mitchell JS, Tucker CG, et al. Interferon-gamma drives programmed death-ligand 1 expression on islet beta cells to limit T cell function during autoimmune diabetes. Scientific reports. 2018;8(1):8295.
73. Gaudy C, Clévy C, Monestier S, Dubois N, Préau Y, Mallet S, et al. Anti-PD1 Pembrolizumab Can Induce Exceptional Fulminant Type 1 Diabetes. Diabetes Care. 2015;38(11):e182-3.
74. Mellati M, Eaton KD, Brooks-Worrell BM, Hagopian WA, Martins R, Palmer JP, et al. Anti-PD-1 and Anti-PDL-1 Monoclonal Antibodies Causing Type 1 Diabetes. Diabetes Care. 2015;38(9):e137-8.
75. Fukui A, Sugiyama K, Yamada T, Tajitsu M, Cao X, Nagai J, et al. A Case of Nivolumab-Induced Fulminant Type 1 Diabetes with Steroidsand Glucagon-Like Peptide 1 Administration during the Early Onset. journal of Clinical Case Reports. 2016;2016.
76. Kapke J, Shaheen Z, Kilari D, Knudson P, Wong S. Immune Checkpoint Inhibitor-Associated Type 1 Diabetes Mellitus: Case Series, Review of the Literature, and Optimal Management. Case Rep Oncol. 2017;10(3):897-909.
77. Zaied AA, Akturk HK, Joseph RW, Lee AS. New-onset insulin-dependent diabetes due to nivolumab. Endocrinol Diabetes Metab Case Rep. 2018;2018.
78. Wedekind MF, Denton NL, Chen CY, Cripe TP. Pediatric Cancer Immunotherapy: Opportunities and Challenges. Paediatr Drugs. 2018;20(5):395-408.
79. Clotman K, Janssens K, Specenier P, Weets I, De Block CEM. Programmed Cell Death-1 Inhibitor-Induced Type 1 Diabetes Mellitus. The Journal of clinical endocrinology and metabolism. 2018;103(9):3144-54.
80. Noble JA, Valdes AM. Genetics of the HLA region in the prediction of type 1 diabetes. Curr Diab Rep. 2011;11(6):533-42.
81. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383(9911):69-82.
82. Noble JA, Valdes AM, Varney MD, Carlson JA, Moonsamy P, Fear AL, et al. HLA class I and genetic susceptibility to type 1 diabetes: results from the Type 1 Diabetes Genetics Consortium. Diabetes. 2010;59(11):2972-9.

83. Magis Q, Gaudy-Marqueste C, Basire A, Loundou A, Malissen N, Troin L, et al. Diabetes and Blood Glucose Disorders Under Anti-PD1. J Immunother. 2018;41(5):232-40.
84. Sood A, Cole D, Abdollah F, Eilender B, Roumayah Z, Deebajah M, et al. Endocrine, Sexual Function, and Infertility Side Effects of Immune Checkpoint Inhibitor Therapy for Genitourinary Cancers. Curr Urol Rep. 2018;19(9):68.
85. Brunet-Possenti F, Opsomer MA, Gomez L, Ouzaid I, Descamps V. Immune checkpoint inhibitors-related orchitis. Ann Oncol. 2017;28(4):906-7.
86. Quach HT, Robbins CJ, Balko JM, Chiu CY, Miller S, Wilson MR, et al. Severe Epididymo-Orchitis and Encephalitis Complicating Anti-PD-1 Therapy. Oncologist. 2019;24(7):872-6.
87. Bai X, Lin X, Zheng K, Chen X, Wu X, Huang Y, et al. Mapping endocrine toxicity spectrum of immune checkpoint inhibitors: a disproportionality analysis using the WHO adverse drug reaction database, VigiBase. Endocrine. 2020;69(3):670-81.
88. Scovell JM, Benz K, Samarska I, Kohn TP, Hooper JE, Matoso A, et al. Association of Impaired Spermatogenesis With the Use of Immune Checkpoint Inhibitors in Patients With Metastatic Melanoma. JAMA Oncol. 2020;6(8):1297-9.
89. Jacobo P, Guazzone VA, Theas MS, Lustig L. Testicular autoimmunity. Autoimmun Rev. 2011;10(4):201-4.
90. Hedger MP, Meinhardt A. Cytokines and the immune-testicular axis. J Reprod Immunol. 2003;58(1):1-26.
91. Schuppe HC, Meinhardt A. Immune privilege and inflammation of the testis. Chem Immunol Allergy. 2005;88:1-14.
92. Pérez CV, Sobarzo CM, Jacobo PV, Pellizzari EH, Cigorraga SB, Denduchis B, et al. Loss of occludin expression and impairment of blood-testis barrier permeability in rats with autoimmune orchitis: effect of interleukin 6 on Sertoli cell tight junctions. Biol Reprod. 2012;87(5):122.
93. Jacobo P. The role of regulatory T Cells in autoimmune orchitis. Andrologia. 2018;50(11):e13092.
94. P. J. Rowe FC, T. B. Hargreave and A. Mahmoud. WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male. Cambidge University Press. 2000:102.
95. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018;36(19):1994-2001.
96. Haddad N, Vidal-Trecan T, Baroudjian B, Zagdanski AM, Arangalage D, Battistella M, et al. Acquired generalized lipodystrophy under immune checkpoint inhibition. Br J Dermatol. 2020;182(2):477-80.
97. Jehl A, Cugnet-Anceau C, Vigouroux C, Legeay AL, Dalle S, Harou O, et al. Acquired Generalized Lipodystrophy: A New Cause of Anti-PD-1 Immune-Related Diabetes. Diabetes Care. 2019;42(10):2008-10.
98. Nalluru SS, Piranavan P, Ning Y, Ackula H, Siddiqui AD, Trivedi N. Hypocalcemia with Immune Checkpoint Inhibitors: The Disparity among Various Reports. International journal of endocrinology. 2020;2020:7459268.
99. Deligiorgi MV, Siasos G, Vergadis C, Trafalis DT. Central diabetes insipidus related to anti-programmed cell-death 1 protein active immunotherapy. Int Immunopharmacol. 2020;83:106427.
100. Fosci M, Pigliaru F, Salcuni AS, Ghiani M, Cherchi MV, Calia MA, et al. Diabetes insipidus secondary to nivolumab-induced neurohypophysitis and pituitary metastasis. Endocrinol Diabetes Metab Case Rep. 2021;2021.
101. Zhao C, Tella SH, Del Rivero J, Kommalapati A, Ebenuwa I, Gulley J, et al. Anti-PD-L1 Treatment Induced Central Diabetes Insipidus. The Journal of clinical endocrinology and metabolism. 2018;103(2):365-9.
102. Abdulla H. Primary hyperparathyroidism: molecular genetic insights and clinical implications. Society for Endocrinology BES 2017; Harrogate, UK: Bioscientifica; 2017.
103. Desikan SP, Varghese R, Kamoga R, Desikan R. Acute hyponatremia from immune checkpoint inhibitor therapy for non-small cell lung cancer. Postgrad Med J. 2020;96(1139):570-1.
104. Kosche C, Mohindra N, Choi JN. Vitiligo in a patient undergoing nivolumab treatment for non-small cell lung cancer. JAAD Case Rep. 2018;4(10):1042-4.
105. 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 Mar;51(3):145-156. doi: 10.1055/a-0843-3366. Epub 2019 Mar 12. PMID: 30861560.