Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints

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ABSTRACT Immune checkpoints are small molecules expressed by immune cells that play critical roles in maintaining immune homeostasis. Targeting the immune checkpoints cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1) with inhibitory antibodies has demonstrated effective and durable antitumor activity in subgroups of patients with cancer. The US Food and Drug Administration has approved several immune checkpoint inhibitors (ICPis) for the treatment of a broad spectrum of malignancies. Endocrinopathies have emerged as one of the most common immune-related adverse events (irAEs) of ICPi therapy. Hypophysitis, thyroid dysfunction, insulin-deficient diabetes mellitus, and primary adrenal insufficiency have been reported as irAEs due to ICPi therapy. Hypophysitis is particularly associated with anti-CTLA-4 therapy, whereas thyroid dysfunction is particularly associated with anti-PD-1 therapy. Diabetes mellitus and primary adrenal insufficiency are rare endocrine toxicities associated with ICPi therapy but can be life-threatening if not promptly recognized and treated. Notably, combination anti-CTLA-4 and anti-PD-1 therapy is associated with the highest incidence of ICPi-related endocrinopathies. The precise mechanisms underlying these endocrine irAEs remain to be elucidated. Most ICPi-related endocrinopathies occur within 12 weeks after the initiation of ICPi therapy, but several have been reported to develop several months to years after ICPi initiation. Some ICPi-related endocrinopathies may resolve spontaneously, but others, such as central adrenal insufficiency and primary hypothyroidism, appear to be persistent in most cases. The mainstay of management of ICPi-related endocrinopathies is hormone replacement and symptom control. Further studies are needed to determine (i) whether high-dose corticosteroids in the treatment of ICPi-related endocrinopathies preserves endocrine function (especially in hypophysitis), and (ii) whether the development of ICPi-related endocrinopathies correlates with tumor response to ICPi therapy. ***(Endocrine Reviews 40: 17 – 65, 2019)***

Over the past several years, immune checkpoint inhibitors (ICPis) have emerged as a powerful new tool in the treatment of cancer. These monoclonal antibodies (mAbs) block immune checkpoints, unleashing T-cells to fight cancer. However, immune checkpoints also play a key role in maintaining immunological self-tolerance and preventing autoimmune disorders, and ICPi therapy can also trigger autoimmune adverse effects, termed immune-related adverse events (irAEs). These irAEs can affect numerous organs in the body. Most commonly, irAEs associated with ICPi therapy involve the skin, colon, liver, lungs, and endocrine organs; less commonly, the kidneys, ocular system, nervous system, cardiovascular system, musculoskeletal system, and hematologic system may be affected (1, 2). Endocrinopathies are among the most common irAEs associated with ICPi therapy and include hypophysitis, thyroid dysfunction, insulin-deficient diabetes mellitus (DM), and primary adrenal insufficiency (PAI) (3). Given the increasing use of ICPi therapy in oncologic practice and the potentially life-threatening nature of endocrinopathies if not promptly recognized and treated, it is critical for endocrinologists and oncologists to be aware of the clinical manifestations, diagnosis, and management of ICPi-related endocrinopathies.

In the first half of this review, we describe the biological functions of immune checkpoints, focusing on cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1). Blockade of these checkpoints can induce endocrinopathies, and we will review our current knowledge of two sources of information that may enhance our understanding of this association: (1) polymorphisms in major genes

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ESSENTIAL POINTS

- Immune checkpoints are small molecules on the surface of immune cells involved in the regulation of the immune response; immune checkpoint inhibitors (ICPis) are antibodies that target certain immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1), resulting in T-cell activation and antitumor activity, and have opened a new era in cancer therapy
- Immune-related adverse events (irAEs) are common complications of ICPi therapy, and endocrinopathies are among the most common irAEs; these include hypophysitis, thyroid dysfunction, insulin-deficient diabetes mellitus, and PAI
- Specific endocrinopathies appear to be more common with specific ICPis; hypophysitis is relatively more common with anti-CTLA-4 agents such as ipilimumab, whereas thyroid dysfunction is relatively more common with anti-PD-1 agents such as nivolumab and pembrolizumab, and combining these agents appears to further increase the risk of ICPi-related endocrinopathies
- Hypophysitis, or inflammation of the pituitary gland, is one of the most common ICPi-related endocrinopathies and is mainly associated with anti-CTLA-4 therapy; it can cause headache and fatigue, can result in temporary or permanent deficiencies in one or more pituitary hormones, and can manifest as pituitary enlargement on imaging, and is managed with hormone replacement and supportive care
- Thyroid dysfunction is also one of the most common ICPi-related endocrinopathies and is mainly associated with anti-PD-1 therapy and combination anti-PD-1 and anti-CTLA-4 therapy; it can present as hypothyroidism or transient thyrotoxicosis followed by hypothyroidism, symptoms are typically nonspecific and mild, and management includes beta-blockers as needed for symptomatic thyrotoxicosis and thyroid hormone replacement with levothyroxine for hypothyroidism
- Insulin-deficient diabetes mellitus and PAI are infrequent ICPi-related endocrinopathies but can result in life-threatening diabetic ketoacidosis or adrenal crisis, respectively, without prompt diagnosis and proper management
- The time to onset of ICPi-related endocrinopathies generally ranges from weeks to months after the initial dose of ICPi therapy; further studies are needed to determine (i) whether high-dose corticosteroids in the treatment of ICPi-related endocrinopathies preserve endocrine function, and (ii) whether the development of ICPi-related endocrinopathies correlates with tumor response to ICPi therapy

involved in these immune checkpoints that are associated with autoimmune endocrinopathies, and (2) autoimmune phenotypes that occur after the deletion or blockade of immune checkpoints in animal studies. In the second half of this Review, we will describe the pathophysiology, clinical manifestations, diagnosis, and management of ICPi-related endocrinopathies, specifically hypophysitis, thyroid dysfunction, insulin-deficient DM, and PAI.

Biological Functions of Immune Checkpoints

Immune checkpoints are small molecules present on the cell surface of T-lymphocytes (4). These small molecules play critical roles in maintaining immune homeostasis and self-tolerance and modulating the duration and amplitude of physiological immune responses. Some immune checkpoints, such as CD28, ICOS, CD137, OX40, and CD27, mediate stimulatory signals to enhance T-cell activity. Others, such as CTLA-4, PD-1, LAG3, TIMs, and BTLA, mediate inhibitory signals to blunt T-cell activity (4). In this section, we will review the biological profiles of two immune checkpoints, CTLA-4 and PD-1. Several mAbs targeting CTLA-4, PD-1, and PD-L1 (a ligand of PD-1) have been approved by the US Food and Drug Administration (FDA) for the treatment of advanced malignancies. These antibodies are associated with endocrine toxicities.

CTLA-4

CTLA-4 is a glycoprotein expressed by both CD4+ and CD8+ T-cells (Box 1). The *CTLA-4* gene was identified in 1987 by screening mouse cytolytic T-cell-derived cDNA libraries (5), and the transcript of this gene was found in cytotoxic T-cells (5–7). The human *CTLA-4* gene was subsequently cloned and mapped (8), and the human CTLA-4 protein shares 76% homology with the mouse CTLA-4 protein. The human *CTLA-4* gene maps to the same chromosomal region (chromosome 2, q33-q34) as CD28 and is structurally homologous to CD28. Both are membrane proteins and members of the immunoglobulin (Ig) superfamily and are categorized as a subgroup of membrane-bound single V domains. A CTLA-4-immunoglobulin fusion protein (CTLA-4-Ig) was found to bind specifically to B7-transfected Chinese hamster ovary cells and lymphoblastoid cells and immunoprecipitated B7 from ^{125}I-labeled cell surface extracts of these cells (7). CD28 stimulates T-cell activity, promoting IL-2 production, clonal expansion, anergy avoidance, and effector function (9, 10). Initially, given the chromosomal proximity and close structural relationship of CTLA-4 and CD28, it was thought that these two genes could be the result of the duplication of a common evolutionary precursor and may share functional properties (11). However, evidence emerged that CTLA-4 and CD28 have opposing effects on T-cell activity (12). CTLA-4-Ig inhibits immune responses *in vivo*. CTLA-4 binds to

BOX 1. Key points regarding CTLA-4

- CTLA-4 is a glycoprotein that is structurally homologous to CD28.
- CTLA-4 and CD28 share the ligands CD80 and CD86.
- Unlike CD28, CTLA-4 inhibits conventional T-cell activity.
- CTLA-4 is constitutively expressed on the cell surface of regulatory T-cells (Tregs).
- CTLA-4 expression on the surface of conventional T-cells is inducible.
- CTLA-4 inhibits T-cell activation by intrinsic mechanisms, including ligand-dependent/independent inhibitory signaling, ligand completion, and increased adhesion, and stop signal inhibition.
- CTLA-4 also inhibits T-cell activation by extrinsic mechanisms, including induction of indoleamine 2,3-dioxygenase (IDO) through CTLA-4 ligands, induction of inhibitory cytokines through CTLA-4, restriction of ligand availability, and ligand capture from antigen-presenting cells undergoing *trans*-endocytosis to remove ligands from the cell surface.
- CTLA-4 inhibits conventional T-cell activity through its signaling in Tregs.

the same ligands (CD80 and CD86) as CD28 but with a higher binding affinity (13, 14). In contrast to CD28 binding, CTLA-4 binding results in inhibition of IL-2 production, IL-2 receptor expression, and cell cycle progression of activated T-cells and leads to abortion of T-cell activation (15, 16). In addition, CTLA-4 blockade prevents the induction of anergy (17). These studies suggested that CTLA-4 plays an inhibitory role in the regulation of T-cell activity.

The inhibitory role of CTLA-4 in T-cell responses is further supported by animal studies. Deletion of CTLA-4 in mice leads to fatal lymphoproliferative disease, and these mice die by 3 to 4 weeks of age (18, 19). In contrast, CD28-deficient mice are immunocompromised (20). The inhibitory effects of CTLA-4 seem to depend on the presence and availability of its ligands, CD80 and CD86. Blocking CD80 and CD86 using CTLA-4-Ig prevented increased autoimmunity in CTLA-4-deficient (CTLA-$4^{-/-}$) mice (21). When CTLA-4-Ig treatment is terminated, CTLA-$4^{-/-}$ T-cells become activated and lymphoproliferative disease recurs. The coordination of CTLA-4 and its ligands is further supported by crossing CTLA-4-deficient mice with mice deficient in B7-1 (CD80) and B7-2 (CD86) to generate mice with a triple deletion of CTLA-4, CD80, and CD86. Mice lacking CTLA-4, CD80, and CD86 have a normal lifespan and do not have lymphocytic infiltrates in any organs or increased T-cell activation (22). Mice with haploinsufficiency of CTLA-4 have no obvious phenotypic changes (19, 23). In contrast, CTLA-4 haploinsufficiency in humans appears to have a more profound phenotype. A heterozygous nonsense mutation in exon 1 of *CTLA-4* in humans is related to an autosomal dominant immune dysregulation syndrome characterized by hypogammaglobulinemia, recurrent infections, and multiple autoimmune clinical features (24). Additionally, heterozygous germline mutations of *CTLA-4* in six patients from four unrelated families caused dysregulation of FoxP3+ Tregs, hyperactivation of effector T-cells, and lymphocytic infiltration of target organs (25). The mechanisms underlying this phenotypic discrepancy between human and mice are not known. However, the types of exposures experienced by humans who live in the community are different from the exposures that mice in the laboratory setting experience (26).

CTLA-4 expression occurs in both Tregs and conventional T-cells. It is constitutively expressed in Tregs, but its expression and cell surface trafficking in conventional T-cells is induced during activation of the cells (27–29). In conventional T-cells, CTLA-4 spends most of its time in the intracellular pool (30). Intracellular CTLA-4 vesicles interact with the $\mu 2$ subunit of the clathrin adaptor protein complex AP2 to mediate CTLA-4 trafficking between the intracellular pool and the cell surface (31–34). T-cell receptor (TCR) activation promotes the trafficking of CTLA-4 from the intracellular pool to the cell surface (35), where CTLA-4 interacts with its ligands. Concurrently, rapid and constitutive endocytosis of CTLA-4 from the cell surface to the intracellular pool or to lysosomes for degradation keeps only a small portion of CTLA-4 on the cell surface (29, 36). CTLA-4's carboxyl terminal, which is responsible for trafficking, is highly conserved among mammals (37), suggesting important roles of CTLA-4 trafficking and recycling between the cell surface and intracellular compartments in the regulation of CTLA-4 action. These findings suggest that CTLA-4 cell surface expression on conventional T-cells is a reactive response to T-cell activation and is a crucial subsequent step to leash conventional T-cell activation. An interruption of CTLA-4 trafficking may lead to increased autoimmunity; however, there have been no reports that describe a defect of CTLA-4 trafficking and resultant autoimmune disease.

The role of Treg CTLA-4 in the regulation of cytotoxic T-cell activity remains controversial. CTLA-4-deficient cells showed a reduction in suppressive capacity in CD4+CD25+ thymocytes from CTLA-4-deficient mice and bone marrow chimeric mice (37–39). On the other hand, Tregs isolated from anti-CTLA-4 antibody-treated mice or human and

TCR-transgenic CTLA-4-deficient mice displayed intact inhibitory effects on T-effector cell activations (40–43). The study by Kong *et al.* (44) suggests an important role of a complex of CTLA-4 cytoplasmic domain with the kinase PKC-η in the regulation of activities of Tregs, as well as in controlling CTLA-4 cell biology and function. Overexpression of CTLA-4 in human conventional T-cells suppressed T-cell activation, supporting the relationship between CTLA-4 expression and its inhibitory activity in conventional T-cells (45).

CTLA-4 obviously plays a key inhibitory role in the regulation of the balance between T-cell activation and tolerance, but the mechanisms by which CTLA-4 mediates its inhibitory functions remain unclear. Both intrinsic and extrinsic mechanisms have been proposed (Fig. 1) (46). Intrinsically, CTLA-4 can inhibit conventional T-cell activation by mediating ligand-dependent or ligand-independent inhibitory signaling, outcompeting CD28 for B7 ligand binding, increasing adhesion, or inhibiting stop signals (37). Extrinsic effects of CTLA-4 were suggested by the generation of bone marrow chimeric mice that have a mixture of CTLA-4 wild type and CTLA-4-deficient cells. Chimeric mice that contain a mixture of wild-type and CTLA-4-deficient cells develop normal immune systems, and CTLA-4-deficient cells do not become spontaneously activated in the presence of cells that express CTLA-4 (47–50), suggesting that CTLA-4 on one T-cell may inhibit the activation of a CTLA-4-deficient cell in a cell-extrinsic fashion. Additionally, CTLA-4 can initiate reverse signals through its ligands CD80 and CD86 on antigen-presenting cells (APCs). The reverse signal results in activation of the tryptophan-degrading enzyme IDO in APCs, stimulating the production of regulatory cytokines such as TGF-β and leading to inhibition of APCs or T-cells. Soluble CTLA-4 can occupy CD80 and CD86 to restrict ligand availability to CD28. CTLA-4 can capture its ligands CD80 and CD86 from APCs and remove them by undergoing endocytosis (*trans*-endocytosis), thereby reducing their availability for CD28 engagement (Fig. 1) (37).

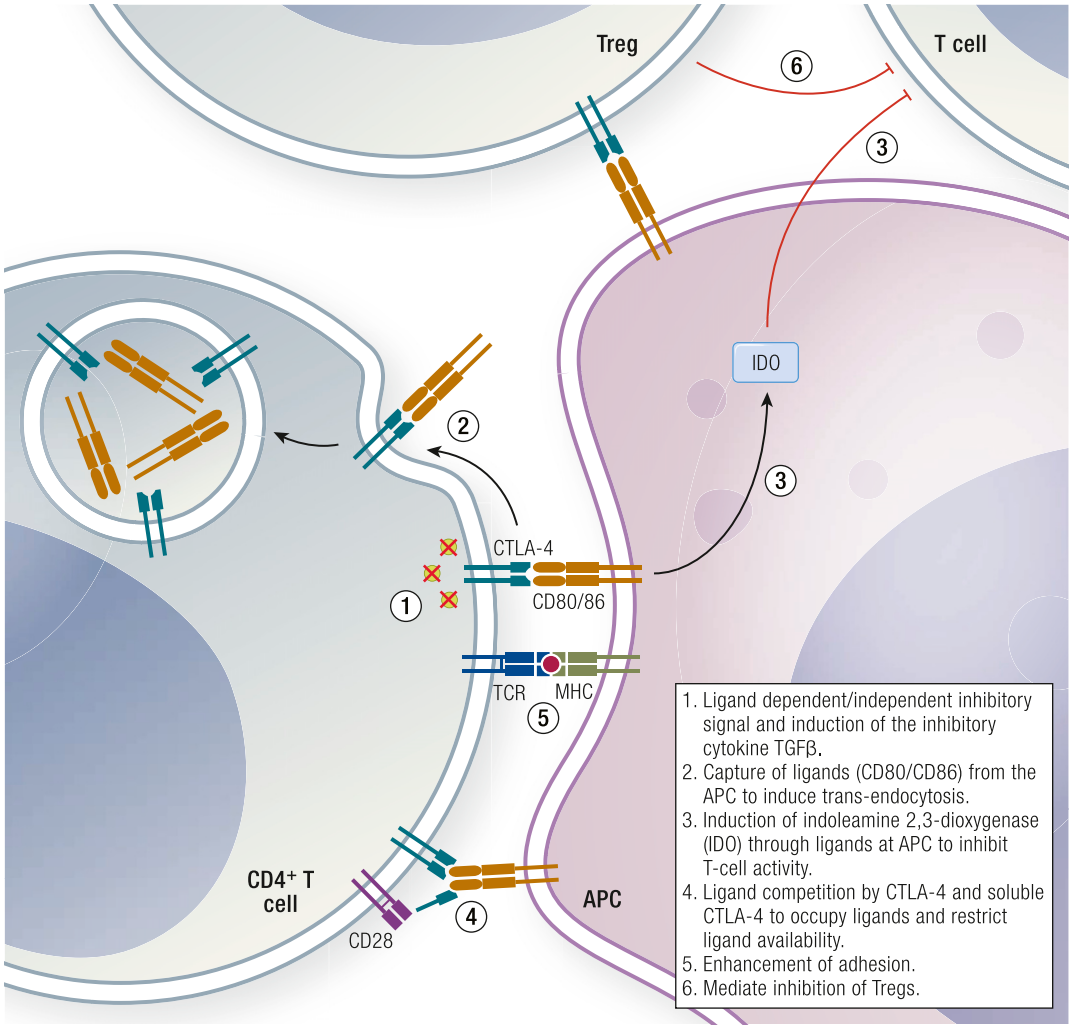


Figure 1. Model of intrinsic and extrinsic actions of CTLA-4. CTLA-4 inhibits T-cell activity by a number of intrinsic and extrinsic mechanisms. CTLA-4 expressed on conventional T-cells interacts with its ligands CD80 and CD86 to initiate inhibitory signaling, enhance adhesion, and compete with CD28 to block interaction between CD28 and CD80/CD86. CTLA-4 can deplete its ligands (CD80 and CD86) by removing them from APCs through *trans*-endocytosis. CTLA-4 can also act as a ligand to activate CD80 and CD86 on APCs to induce IDO, stimulate the production of regulatory cytokines such as TGF-β, and trigger APC or T-cell inhibition. CTLA-4 on Tregs enhances the inhibitory action of Tregs on conventional T-cells. MHC, major histocompatibility complex. [© 2019 Illustration Presentation ENDOCRINE SOCIETY].

In summary, CTLA-4 acts as an inhibitory immune checkpoint to inhibit T-cell activity. The mechanisms of its actions on conventional T-cells and Tregs are complex and remain to be elucidated.

BOX 2. Key points regarding PD-1

- Like CTLA-4, PD-1 belongs to the CD28 family within the Ig superfamily, but it is an outlier within the CD28 family.
- PD-1 does not share ligands with CD28 but instead has its own specific ligands, PD-L1 and PD-L2.
- PD-1 is expressed on many types of cells, including T-cells, B-cells, macrophages, and some dendritic cells.
- PD-1 cell surface expression is low but is increased by T-cell activation or chronic infections, such as HIV.
- Engagement of PD-1 by its ligands during TCR signaling can block T-cell proliferation, cytokine production, and cytolytic function and impair T-cell survival.
- PD-1 signaling inhibits protein kinase B (Akt) phosphorylation by preventing CD28-mediated activation of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K).
- PD-1 also inhibits several other intracellular signaling pathways.

PD-1

PD-1 is a glycoprotein that was first identified by a Japanese group in 1992 (Box 2) (51). The gene was named *PD-1* because its expression was found to be upregulated in a T-cell hybridoma undergoing programmed death or apoptosis (51). Its key role in the regulation of T-cell activity was subsequently recognized. Like CTLA-4, PD-1 belongs to the CD28 family within the Ig superfamily. PD-1 consists of an *N*-terminal IgV-like domain, an approximately 20-amino acid stalk separating the IgV-like domain from the plasma membrane, a transmembrane domain, and a cytoplasmic domain (51–53). In contrast to CD28 and CTLA-4, which share a similar general structure, PD-1 is more of an outlier within the CD28 family. Unlike *CD28* and *CTLA-4*, which are genomic neighbors (mapping to chromosome 2q33), *PD-1* is located on a different region of chromosome 2 (2q37). PD-1 is less conserved in terms of its cytoplasmic tails than CD28 and CTLA-4. The cytoplasmic tails of mouse and human CD28 and CTLA-4 share 79% and 100% amino acid sequence homology, respectively. In contrast, the human PD-1 cytoplasmic tail shares only 59% homology with its murine counterpart. Unlike CD28 and CTLA-4, which form dimers on cell surfaces, PD-1 exists as monomers (54, 55), reflecting its unique intracellular signaling mechanisms. The cytoplasmic tail of PD-1, like that of other CD28 family members, has no intrinsic enzymatic activity (56). Rather, its tail serves as an adapter for signaling molecules recruited to the cell membrane following phosphorylation of tyrosine residues in the tail. Additionally, in contrast to the cytoplasmic tail of other CD28 family members, the cytoplasmic tail of PD-1 does not contain SH2 and SH3 binding motifs. Instead, it has a tyrosine-containing immunoreceptor motif and an immunoreceptor tyrosine-based inhibition motif, defined as V/I/LxYxxL, followed by an immunoreceptor tyrosine-based switch motif, defined as TxYxxL (56). Furthermore, unlike CD28 and CTLA-4, which share the same ligands CD80 and CD86, PD-1 has its own specific ligands, PD-L1 and PD-L2.

TCR engagement initiates the T-cell response in terms of gene expression, cell proliferation, and effector function. Engagement of PD-1 by its ligands during TCR signaling can block T-cell proliferation, cytokine production, and cytolytic function and impair T-cell survival (56). In the setting of TCR engagement, costimulatory molecule binding activates phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and its downstream target Akt, resulting in increased glucose uptake through increasing glucose transporters on the plasma membrane and upregulating glycolytic enzyme activity to provide fuel for cell proliferation and effector function (Fig. 2) (57). PD-1 signaling inhibits Akt phosphorylation by preventing CD28-mediated activation of PI3K (58). The ability of PD-1 to attenuate PI3K/Akt activation relies on its immunoreceptor tyrosine-based switch motif interaction with Src-homology 2 domain-containing phosphatases 1 and 2 (58–61). Consequently, PD-1 binding with its ligands PD-L1 or PD-L2 suppresses T-cell activity by reducing fuel supply through inhibition of the PI3K/Akt pathway to block glucose uptake. Compared with CTLA-4, PD-1 inhibits T-cell activation to a greater extent in terms of its effects on gene expression induced by CD4+ T-cell activation (58). Indeed, the binding of CTLA-4 with its ligands does not inhibit costimulation-mediated PI3K signaling. In addition to its inhibitory effect on the PI3K/Akt pathway, the binding of PD-1 with its ligands blunts phosphorylation of CD3ζ, ζ-associated protein of 70 kDa, and protein kinase Cθ (58). PD-1 engagement also inhibits extracellular signal-regulated kinase activation, but this effect can be overcome through cytokine receptor signaling, particularly through cytokines that activate signal transducer and activator of transcription 5, such as IL-2, IL-7, and IL-15 (62). Moreover, PD-1 engagement can prevent the induction of the cell survival factor B-cell lymphoma-extra large as well as expression of transcription factors associated with effector cell function, including transcription factor GATA-3 and T-box transcription factors such as T-bet and eomesodermin (Eomes) (63, 64). These findings underscore the differences in cell signaling mediated by PD-1 and CTLA-4. These differences may account at least in part for the different clinical manifestations of autoimmunity seen by blocking PD-1 or CTLA-4.

PD-1 levels on the cell surface of resting T-cells from healthy individuals are barely detectable. The expression and cell surface presentation of PD-1 are inducible upon activation of T-cells (63). In addition, in functionally impaired antigen-specific T-cells (exhausted T-cells), typically seen in many chronic

infections such as HIV infection, PD-1 expression is significantly increased (65, 66). Treating mice with chronic viral infections with anti-PD-L1 antibody restores CD8 T-cell function and reduces viral load (65). In an *in vitro* experiment using fresh blood samples collected from patients with HIV, blockade of the PD-1/PD-L1 pathway by anti-PD-L1 antibody improved HIV-specific CD4 and CD8 T-cell function (66). Unlike CTLA-4, which is primarily expressed on T-cells, PD-1 is found on T-cells, B-cells, macrophages, and some dendritic cells (52, 67, 68). PD-1 conveys its inhibitory signal when engaged along with the TCR on T-cells or the B-cell receptor on B-cells (52, 63). PD-1 also constrains macrophage and dendritic cell responses to toll-like receptor agonists and microbes (67, 69).

As noted, PD-1 has two specific ligands, PD-L1 and PD-L2. PD-L1 (B7-H1) was identified in 2000 by two independent groups (70, 71). The following year, PD-L2 was identified (60). Both PD-1 ligands belong to the type 1 transmembrane protein family, with IgV- and IgC-like domains in the extracellular region (72). It is important to note that the expression of PD-L1 is universal. PD-L1 was identified in lymphoid tissue including T-cells, APCs such as dendritic cells, macrophages/monocytes, and B-cells. PD-L1 is also found in nonlymphoid cells such as vascular endothelial cells, thyroid cells, muscle cells, hepatocytes, placental cells, mesenchymal stem cells, and pancreatic islet cells (73–76). Indeed, expression of PD-L1 in peripheral tissues plays a critical role in preventing autoimmune-induced tissue damage (74). Notably, cancer cells and virus-infected cells express PD-L1 (72). Expression of PD-L1 on tumor cells is a mechanism by which they escape detection by the host immune system (77). Various solid tumor cells, including renal cell carcinoma, nonsmall cell carcinoma, thymoma, ovarian cancer, and colorectal cancer, use PD-L1 expression as an immune shield to generate an immunosuppressive tumor microenvironment and avoid T-cell attack (77–79). Indeed, high expression of PD-L1 in tumor tissues predicts a poorer prognosis (80–83). Further, blocking the interaction between PD-1 and PD-L1 with antibodies generates a significantly better response in PD-L1-positive tumors (84–87). PD-L2 is primarily expressed on APCs, including dendritic cells and macrophages (88). The biological function of PD-L2 appears to overlap with that of PD-L1, but PD-L2 acts mainly through the dampening and regulation of Th2-driven T-cell immune responses both during the induction phase and the effector phase (89).

In summary, PD-1 belongs to the CD28 family within the Ig superfamily but has several unique features that make it more of an outlier within the CD28 family. PD-1 binds with its own unique ligands (PD-L1 and PD-L2) and is expressed in peripheral tissues or APCs to activate inhibitory signaling pathways to suppress the immune response.

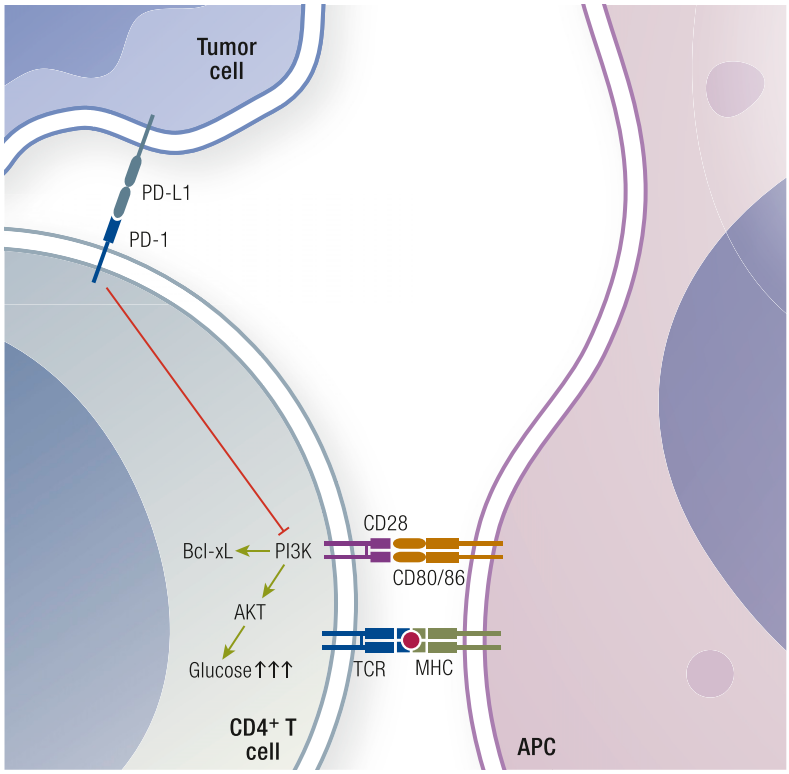


Figure 2. Mechanisms of PD-1 action on T-cells. Engagement of PD-1 with its ligand PD-L1 induces an intracellular inhibitory pathway to inhibit costimulatory CD28-activated PI3K pathways. As a result, gluconeogenesis and glucose uptake decrease, leading to T-cell exhaustion. Bcl-xL, B-cell lymphoma-extra large; PD-L1, programmed death-ligand 1. [© 2019 Illustration Presentation ENDOCRINE SOCIETY].

Autoimmune Endocrinopathies in Patients With *CTLA-4* or *PD-1* Polymorphisms

CTLA-4 polymorphisms and autoimmune endocrinopathies

The association of *CTLA-4* polymorphisms with autoimmune endocrinopathies is well documented (Box 3) (90, 91). In a study comparing 133 white patients with Graves disease with 85 controls, an increased frequency of a single allele of an (AT)n repeat sequence within the 3′ untranslated region (UTR) of exon 4 of *CTLA-4* was found, with an OR for development of disease of 2.82 (92). Importantly, this microsatellite of an (AT)n repeat sequence within the 3′ UTR is not present in mouse *CTLA-4* and is in a region of lowest sequence similarity between mouse and human *CTLA-4* (93). A study from the United Kingdom analyzed this microsatellite in 112 patients with Graves disease, 44 patients with autoimmune hypothyroidism, and 91 controls without autoimmune thyroid disease (AITD) and found that the frequency of allele 106 of the *CTLA-4* microsatellite was significantly more common in patients with Graves

BOX 3. Key points regarding *CTLA-4*, *PD-1*, *PD-L1*, and *PD-L2* polymorphisms

- *CTLA-4* polymorphisms are associated with autoimmune endocrinopathies, including type 1 DM (T1DM), Graves disease, autoimmune hypothyroidism, and Addison disease.
- The *CTLA-4* single nucleotide polymorphisms (SNPs) CT60, JO31, JO30, and 49A/G are commonly associated with these autoimmune endocrinopathies.
- Associations of *PD-1* polymorphisms with autoimmune endocrinopathies are infrequently reported.
- A few studies suggest a linkage of *PD-1* polymorphisms with T1DM.
- *PD-L1* polymorphisms are linked to T1DM, Graves disease, and Addison disease.
- No reports have linked *PD-L2* polymorphisms to autoimmune endocrinopathies.

disease and autoimmune hypothyroidism compared with controls (94). The association of Graves disease with the microsatellite polymorphism *CTLA-4* (AT)n within the *CTLA-4* gene, the G allele of the *CTLA-4* exon 1 SNP, and *CTLA-4* (49)A/G were replicated by several case-control studies and two family-based association studies (95). In European and Asian populations, *CTLA-4* SNPs such as CT60, JO31, JO30, and JO27_1 are associated with Graves disease and Hashimoto thyroiditis (90–92, 96–98). Ethnic differences in AITD susceptibility to *CTLA-4* polymorphisms have also been reported. Three SNPs (CT60, JO31, and JO30) that map to the 3′ UTR of the *CTLA-4* gene were strongly associated with AITD in whites (90). On the other hand, the *CTLA-4* SNPs CT60 but not JO30 have strong links to AITD in Japanese (99). In a recent study, *CTLA-4* SNPs +49A/G and CT60 were found to be associated with Graves disease in Chinese adults and children (OR, 1.5 in adults and 1.42 in children for +49A/G; OR, 1.63 in adults and 1.58 in children for CT60) (100). Although studies support a link between *CTLA-4* polymorphisms and Graves disease, the role of *CTLA-4* polymorphisms in Graves orbitopathy is not clear. Carriers of the G allele of the *CTLA-4* exon 1 SNP had an increased risk of Graves orbitopathy in whites (101) and continental Italians (102). However, several case-control studies in different populations (German, United Kingdom, North American, European, and Japanese) failed to confirm an association between *CTLA-4* gene polymorphisms and Graves orbitopathy (94, 103–106).

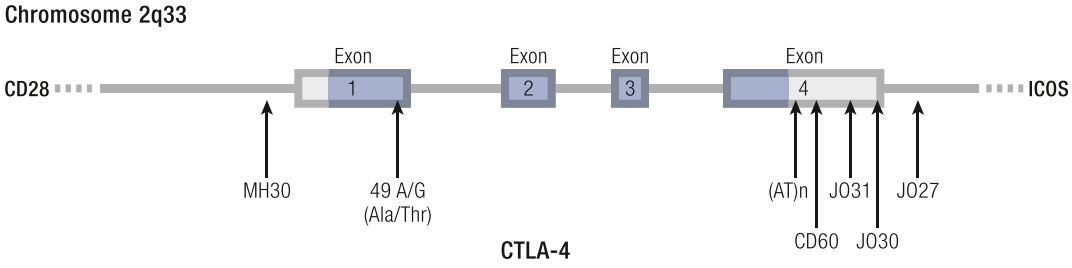
A relationship between *CTLA-4* polymorphisms and T1DM was first reported in a small cohort of Italian multiplex families (107). This finding was followed by numerous transmission disequilibrium analyses and case-control studies supporting a strong linkage between *CTLA-4* polymorphisms and T1DM (95). In a study including multiple ethnic groups (Spanish, French, Mexican-American, Chinese, and Korean), *CTLA-4* polymorphisms were found to be associated with T1DM (108). Another study demonstrated that the *CTLA-4* SNPs CTAF343/T, rs1863800/C, MH30/G, +49/G, CT60/G, JO31/G, JO30/G, and JO27_1/T are associated with T1DM (90). A multicenter collaborative study in Japan showed that +6230 G/A polymorphism of *CTLA-4* is significantly associated with coexistence of T1DM and AITD but is not associated with T1DM without AITD. This polymorphism is also strongly associated with positive autoantibodies to both pancreatic islets and the thyroid (109). In addition to an association with T1DM and AITD, an association of *CTLA-4* SNP CT60 with Addison disease has been reported (110). Importantly, a particularly strong association of *CTLA-4* polymorphisms was shown in Addison disease coexisting with T1DM and/or AITD (type 2 polyglandular autoimmune syndrome) (111). Brozzetti *et al.* (112) evaluated the association between *CTLA-4* polymorphisms and Addison disease in Italians and performed a meta-analysis of five case-control studies. The results showed a substantial linkage between the *CTLA-4* (49)A/G polymorphism and Addison disease.

In addition to their linkage to endocrinopathies, *CTLA-4* gene polymorphisms have been associated with a wide range of other autoimmune disorders, including primary biliary cirrhosis (113), multiple sclerosis (114), celiac disease (115), and rheumatoid arthritis (116, 117). These findings highlight the role of *CTLA-4* polymorphisms in the development of autoimmune disorders. Figure 3 displays a map of common SNPs of the *CTLA-4* gene related to autoimmune endocrinopathies (90, 118). As noted in Fig. 3, most disease-associated SNPs do not affect the amino acid sequence of CTLA-4. It is conceivable that SNPs in noncoding areas affect the level of CTLA-4 expression. Indeed, a disease-susceptible SNP CT60 G/G was related to significantly lower CTLA-4 mRNA expression (90). *CTLA-4* SNPs are described in more detail in a study by Ueda *et al.* (90).

PD-1, PD-L1, and PD-L2 polymorphisms and endocrinopathies

PD-1 polymorphisms have been reported in association with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis (119–122). However, reports regarding the association of *PD-1* polymorphisms with autoimmune endocrinopathies are scant. One research group investigated *PD-1* gene polymorphisms in Addison disease and Graves disease but found no association (123). A Danish study evaluated *PD-1* SNPs in 94 children and adolescents with T1DM compared

Figure 3. Approximate map locations of *CTLA-4* SNPs frequently associated with autoimmune endocrinopathies. SNPs present in both coding and noncoding regions. Most SNPs occur in nontranslated regions. The *CTLA-4* gene has four exons, represented by the boxes. Blue boxes represent translated regions. [© 2019 Illustration Presentation ENDOCRINE SOCIETY].



with those in 155 controls. An intronic 7146G/A SNP was found to be associated with the development of T1DM (OR, 1.92) (124). A *PD-1* haplotype was associated with T1DM in Japanese children (125).

Several studies suggest a linkage of *PD-L1* polymorphisms to autoimmune endocrinopathies. *PD-L1* variants (SNP IDs: rs2297137 and rs4143815) are associated with T1DM in Chileans (126). The same study did not find an association between *PD-L2* polymorphisms and T1DM. Three SNPs in the *PD-L1* gene were found in one report to increase susceptibility to Addison disease and Graves disease (127). A Japanese study showed that an A/C polymorphism at position 8923 in *PD-L1* is associated with Graves disease (128). There have been no reports regarding the association between *PD-L2* polymorphisms and autoimmune endocrinopathies. The broad expression of PD-L1 but not PD-L2 (which is expressed only on APCs) could contribute to the stronger association of PD-L1 SNPs with autoimmune endocrinopathies. Additionally, limited studies and small sample sizes may account in part for the variations in these findings.

In summary, although development of autoimmune disease is influenced by complex interactions between many susceptible gene variants and environmental factors, a solid link exists between SNPs of several genes involved in immune checkpoints (*CTLA-4*, *PD-1*, and *PD-L1*) and increased susceptibility to autoimmune endocrinopathies. Of note, however, the association between polymorphisms in genes involved in immune checkpoints and the development of autoimmune endocrinopathies does not necessarily translate to these same polymorphisms being linked to endocrine-related irAEs induced by ICPi therapy. Unlike polymorphisms, which typically result in mild alterations in gene expression or protein function, blockade by antibodies results in significant loss of function in these immune checkpoints. It is therefore not surprising to observe different manifestations of autoimmune endocrinopathies associated with polymorphisms in immune checkpoint genes compared with endocrine toxicities associated with ICPi therapy.

Autoimmune Phenotypes After Deletion or Blockade of Immune Checkpoints in Animal Studies

Effects of CTLA-4 deletion or blockade

After the identification of the *CTLA-4* gene, the role of CTLA-4 in the regulation of T-cell activation remained controversial until a germline CTLA-4-deficient mouse model was created. Mice deficient in CTLA-4 die at the age of 2 to 3 weeks due to massive lymphoproliferation, leading to lymphocytic infiltration and destruction of major organs (18), indicative of the critical role of CTLA-4 in downregulating T-cell activation and maintaining immunologic homeostasis (Box 4). T-cells isolated from CTLA-4-deficient mice proliferated spontaneously and displayed enhanced proliferation when stimulated through TCR (23). As discussed earlier, CTLA-4 is expressed in both conventional T-cells and Tregs. As Tregs negatively

BOX 4. Key points regarding CTLA-4 and PD-1 deletion or blockade

- Deletion of CTLA-4 in mice results in massive lymphoproliferation and premature death.
- Selective germline CTLA-4 deletion in murine Tregs leads to systemic lymphoproliferation and fatal T-cell-mediated autoimmune disease, underscoring the important role of CTLA-4 in Tregs.
- In contrast, deletion of CTLA-4 in Tregs during adulthood leads to resistance to autoimmunity, underscoring unique roles of CTLA-4 in Tregs during embryonic development and adulthood.
- PD-1 deletion in C57BL/6(B6) mice leads to lupus-like proliferative arthritis and glomerulonephritis.
- Deletion of PD-1 in BALB/c mice leads to premature death due to autoimmune cardiomyopathy.
- PD-1 deletion in nonobese diabetic (NOD) mice accelerates the onset and frequency of T1DM.

regulate conventional T-cell activity, expression of CTLA-4 in Tregs raised the question of what CTLA-4's action in Tregs is. Using transgenic techniques to selectively delete CTLA-4 in Tregs has provided insight. Selective CTLA-4 deficiency in Tregs results in spontaneous development of systemic lymphoproliferation, fatal T-cell-mediated autoimmune disease, hyperproduction of IgE in mice, and potent tumor immunity (129), indicating Treg suppressive function requires CTLA-4 expression. Further studies demonstrated that CTLA-4 deletion in Tregs leads to unusual activation and expansion of conventional T-cells. However, CTLA-4 expression in conventional T-cells prevents aberrantly activated T-cells from infiltrating and fatally damaging nonlymphoid tissues (130). These results suggest that CTLA-4 has a dual function in maintaining T-cell tolerance. Surprisingly, CTLA-4 deletion in Tregs during adulthood leads to resistance to autoimmunity (131). These findings underscore distinct roles of CTLA-4 in Tregs during embryonic development and adulthood. Germline deletion of CTLA-4 during adulthood resulted in activation and expansion of both conventional T-cells and Tregs (131).

Antitumor activity by CTLA-4 blockade has been studied extensively in mouse models of solid and hematological tumors, including malignancies of the bladder, brain, breast, colon, lung, ovary, prostate, skin, and blood, as well as in fibrosarcomas, lymphomas, and plasmacytomas (132). However, few studies have evaluated autoimmune adverse events in these mouse models. *In vivo* administration of antibodies against CTLA-4 resulted in complete regression or delayed tumor growth in several types of established transplantable murine tumor models, such as cancer of the ovary, bladder, and brain, and fibrosarcomas (133–138), and prevented breast cancer metastasis in mice (139). Notably, one study found that blockade of CTLA-4 in both effector and Treg compartments contributes to the antitumor activity of anti–CTLA-4 antibodies (140). Iwama *et al.* (141) injected SJL/J mice with a hamster IgG1k mAb blocking murine CTLA-4 using a dose mimicking the regimen used in humans. They found that repeated injections of the CTLA-4-blocking antibody induce hypophysitis (141). A distinct infiltration of the pituitary gland with hematopoietic mononuclear cells was seen in mice treated with anti-CTLA-4 antibody but was not seen in the control group. The infiltrating cells were mainly CD45+ lymphocytes and F4/80+ macrophages. CTLA-4 blockade in mice appears to particularly affect the pituitary but not other organs because no hematopoietic infiltration was seen in the thyroid, liver, colon, or skin (141). The same study also found that injections of anti-CTLA-4 antibody induce the formation of pituitary antibodies against subsets of pituitary lactotroph and corticotroph cells (141). Using a murine model (NOD-$H2^{h4}$) susceptible to the development of iodine-induced thyroiditis, injections of anti-CTLA-4 antibody worsened autoimmune thyroiditis, as assessed by a greater incidence of thyroiditis, a more aggressive mononuclear cell infiltration in the thyroid, and higher thyroglobulin antibody (TgAb) levels when compared with control groups (142).

Effects of PD-1 deletion or blockade

PD-1 deletion in C57BL/6(B6) mice leads to lupus-like proliferative arthritis and glomerulonephritis with predominant IgG3 deposition (143). Notably, phenotypes of PD-1 deletion vary in different strains of mice. PD-1 deletion in BALB/c mice resulted in premature death due to autoimmune cardiomyopathy (144). In contrast, premature death was not observed in B6-PD-$1^{-/-}$ mice (144). In a murine model prone to autoimmune diabetes, PD-1 deletion accelerated the onset and frequency of T1DM, with strong T helper 1 polarization of T-cells infiltrating into pancreatic islets (69). Using antibodies that block PD-1 and PD-L1 but not PD-L2 rapidly precipitated diabetes in prediabetic female NOD mice regardless of age (from 1 to 10 weeks old), although this was most pronounced in the older mice (145). The same study found that CTLA-4 blockade induced disease only in neonates (145). Male NOD mice rarely develop overt diabetes. In contrast, blockade of PD-1 or PD-L1 by antibodies in male NOD mice at 10 weeks of age induced diabetes in 80% after anti-PD-1 and 100% after anti-PD-L1 treatment. Anti-PD-1 treatment did not induce diabetes in younger mice (4 weeks), whereas anti–PD-L1 treatment induced diabetes in 75% of mice by day 14 after initiation of treatment (145). This finding again underscores the functional evolution of PD-1 and its ligands during development. Neither nonobese diabetes-resistant mice nor BALB/c mice developed diabetes after PD-1 or PD-L1 blockade, indicating a difference in effect based on mouse strain (145).

Clinical Use of Cancer Immunotherapy Targeting Immune Checkpoints

mAbs blocking CTLA-4, PD-1, or PD-L1 display an effective and durable anticancer effect across a broad spectrum of advanced malignancies (146, 147). Several of these antibodies have been approved by the US FDA for clinical use as monotherapy, as adjuvant therapy, in combination with other ICPi therapy, and in combination with chemotherapy (Table 1) (146).

Grading of Adverse Events Due to Anticancer Therapy

To standardize the definition of adverse events associated with cancer therapy and provide a consistent way to measure their severity, the National Cancer Institute published the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE comprise the standard

Table 1. Characteristics of FDA-Approved ICPi Therapies

Immune Checkpoint Target	Agent	Trade Name	IgG Class	Company	FDA-Approved Indications as of May 2018
CTLA-4	Ipilimumab	Yervoy	IgG1 (recombinant human)	Bristol-Myers Squibb	Melanoma[a,b]
					Renal cell carcinoma[c]
PD-1	Nivolumab	Opdivo	IgG4 (fully human)	Bristol-Myers Squibb	Melanoma[a,c,d]
					Nonsmall cell lung cancer
					Renal cell carcinoma
					Classical Hodgkin lymphoma
					Head and neck squamous cell cancer
					Urothelial carcinoma
					Microsatellite instability-high or mismatch repair deficient colorectal cancer
					Hepatocellular carcinoma
	Pembrolizumab	Keytruda	IgG4 (recombinant human)	Merck	Melanoma
					Nonsmall cell lung cancer[e]
					Head and neck squamous cell cancer
					Classical Hodgkin lymphoma
					Urothelial carcinoma
					Microsatellite instability-high cancer
					Gastric cancer
PD-L1	Atezolizumab	Tecentriq	IgG1k (recombinant human)	Roche	Urothelial carcinoma
					Nonsmall cell lung cancer
	Avelumab	Bavencio	IgG1 (fully human)	Pfizer	Merkel cell carcinoma
					Urothelial carcinoma
	Durvalumab	Imfinzi	IgG1k (fully human)	AstraZeneca	Urothelial carcinoma
					Nonsmall cell lung cancer

[a]The combination of ipilimumab and nivolumab is approved for the treatment of unresectable or metastatic melanoma.
[b]Ipilimumab at a dose of 10 mg/kg intravenously over 90 min is approved for use in the adjuvant setting for melanoma.
[c]The combination of ipilimumab and nivolumab is approved for the treatment of intermediate or poor risk, previously untreated advanced renal cell carcinoma.
[d]Nivolumab is approved for use in the adjuvant setting for melanoma.
[e]Pembrolizumab is approved for the treatment of nonsmall cell lung cancer either as a single agent or in combination with carboplatin and pemetrexed.

classification and severity grading scale used in cancer therapy clinical trials to categorize the frequency and severity of treatment-related adverse events. They are also used in oncologic clinical practice in managing the administration and dosing of cancer therapy. The CTCAE categorize adverse events into five grades in order of increasing toxicity: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), and grade 5 (death). Several versions have been published. The most recent version, CTCAE version 5.0, is summarized in Table 2 (148). This grading system will be referenced throughout this review.

Clinical Practice Guidelines for the Management of irAEs in Patients Treated With ICPi Therapy

Both the American Society of Clinical Oncology (in conjunction with the National Comprehensive Cancer Network) and the European Society for Medical Oncology have published clinical practice guidelines for the diagnosis and management of irAEs in patients treated with ICPi therapy (1, 2). Our clinical recommendations in this review are largely in line with both of these clinical practice guidelines.

ICPi-related hypophysitis

Introduction

Hypophysitis refers to inflammation of the pituitary gland and is a rare disease (149, 150). Hypophysitis can be categorized based on etiology as primary or secondary and based on histopathology as lymphocytic, granulomatous, xanthomatous, plasmacytic (IgG4-related), or mixed (150, 151). Regarding etiology, primary hypophysitis describes inflammation isolated to the pituitary gland; in contrast, secondary hypophysitis describes pituitary inflammation associated with systemic conditions (such as sarcoidosis, granulomatosis with polyangiitis, hemochromatosis, amyloidosis, or histiocytosis), infections (such as tuberculosis, syphilis, or fungal infections); or medications (such as immunomodulatory drugs, including ICPi agents).

Table 2. Grading System of Specific Endocrine Toxicities as Defined by the National Cancer Institute CTCAE, Version 5.0 (148)

Endocrine Toxicity and Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypophysitis: A disorder characterized by inflammation and cellular infiltration of the pituitary gland	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Hypopituitarism: A disorder characterized by a decrease in production of hormones from the pituitary gland	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL[b]	Life-threatening consequences; urgent intervention indicated	Death
Hypothyroidism: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL[a]	Severe symptoms; limiting self care ADL[b]; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hyperthyroidism: A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL[a]	Severe symptoms; limiting self care ADL[b]; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hyperglycemia: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.	Abnormal glucose above baseline with no medical intervention.	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Adrenal insufficiency: A disorder characterized by the adrenal cortex not producing enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison disease or PAI.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

Adapted from United States National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). 2017; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed 30 May 2018.

Abbreviation: ADL, activities of daily living.

[a]As specified in the CTCAE v5.0, instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b]As specified in the CTCAE v5.0, self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Regarding histopathology, hypophysitis can be described by characteristic infiltration of certain cell types in the pituitary gland (150, 151). Lymphocytic hypophysitis is characterized by diffuse lymphocyte infiltration of the pituitary. Granulomatous hypophysitis is characterized by histiocyte and giant cell infiltration of the pituitary, with formation of granulomas. Xanthomatous hypophysitis is characterized by foamy histiocyte (lipid-rich macrophage) infiltration of the pituitary. Plasmacytic (IgG4-related) hypophysitis is characterized by IgG4-positive plasma cell infiltration of the pituitary.

Lymphocytic hypophysitis is the most common form of hypophysitis and primarily affects women (149, 152, 153). It is associated with pregnancy and often occurs in late pregnancy or in the postpartum period (149). Lymphocytic hypophysitis is also associated with autoimmune disorders in 20% to 50% of cases (152).

Hypophysitis can result in pituitary dysfunction, particularly in the anterior pituitary (adenohypophysis), leading to deficiencies in one or more hormones produced by the anterior pituitary. Central adrenal insufficiency and central hypothyroidism are the two most clinically concerning potential deficiencies; in particular, central adrenal insufficiency, if unrecognized and untreated, can cause life-threatening adrenal crisis due to cortisol deficiency. Hypophysitis is one of the most common endocrine irAEs associated with ICPi therapy (Box 5) (3). Specifically, it is the most common endocrine irAE associated with ipilimumab.

Incidence and epidemiology of ICPi-related hypophysitis

A meta-analysis of 34 studies involving ICPi therapy that reported hypophysitis as an irAE found 85 cases of hypophysitis among 6472 patients (3). Of these cases, 34 were grade 3 or higher (0.5% of total cases). Overall, the incidence of hypophysitis was greatest with combination ipilimumab-nivolumab therapy (6.4%) compared with 3.2% with anti-CTLA-4 therapy, 0.4% with anti-PD-1 therapy, and <0.1% with anti-PD-L1 therapy (Fig. 4). Meta-analysis models of drug-specific effects in studies in advanced melanoma that reported the incidence of hypophysitis found that the predicted incidence of hypophysitis was 8.0% (95% CI, 5.9% to 10.8%) with combination ipilimumab-nivolumab therapy compared with 3.8% (95% CI, 2.7% to 5.2%) with anti-CTLA-4 therapy and 1.1% (95% CI, 0.8% to 1.6%) with anti-PD-1 therapy. Compared with patients who received ipilimumab, patients who received anti-PD-1 therapy were significantly less likely to experience hypophysitis (OR, 0.29; 95% CI, 0.18 to 0.49, $P < 0.001$); in contrast, those who received combination therapy were significantly more likely to experience hypophysitis (OR, 2.2; 95% CI, 1.39 to 3.60, $P = 0.001$). Several large retrospective studies reported higher incidences of ipilimumab-related hypophysitis, ranging from 9% to 13% (154–156); this could reflect differences in hormone monitoring or an increased awareness of this disease.

ICPi-related hypophysitis has been reported at higher rates among men. Caturegli *et al.* (157) reviewed 128 cases of hypophysitis due to anti-CTLA-4 therapy and found that the male-to-female ratio was nearly 4:1. This stands in contrast to lymphocytic hypophysitis, which is more common in women (male-to-female ratio 1:3) (158). The male predominance in ICPi-related hypophysitis is likely accentuated by the fact that ICPi therapy (particularly ipilimumab) has been used often in melanoma, and melanoma occurs at higher rates in men than in women; however, rates of ICPi-related hypophysitis appear to be higher in men even after taking this into

BOX 5. Key points regarding ICPi-related hypophysitis

- Hypophysitis is one of the most common endocrine irAEs associated with ICPi therapy, particularly with ipilimumab.
- ICPi-related hypophysitis typically occurs within several weeks to months after ICPi initiation.
- Symptoms and signs of ICPi-related hypophysitis may be nonspecific and most commonly include headache and fatigue.
- The main clinical sequelae of ICPi-related hypophysitis are deficiencies in one or more pituitary hormones. The most common anterior pituitary hormone deficiencies seen in ICPi-related hypophysitis are deficiencies in TSH (central hypothyroidism), ACTH (central adrenal insufficiency), and FSH and LH (hypogonadotropic hypogonadism). GH deficiency and abnormal prolactin levels (typically low if abnormal) are less common but can be seen as well. Diabetes insipidus (DI) is extremely rare.
- Central hypothyroidism and hypogonadotropic hypogonadism from ICPi may be transient, and pituitary function for these hormonal axes may recover spontaneously. ICPi-related central adrenal insufficiency appears to be permanent in most cases.
- On radiographic imaging, mild to moderate diffuse pituitary enlargement can be seen in most cases of ICPi-related hypophysitis and is a sensitive and specific sign of hypophysitis. Pituitary enlargement typically resolves within several weeks. Mass effect (*e.g.,* impingement of the optic chiasm) is rare.
- Treatment involves supportive management and hormone replacement with levothyroxine, corticosteroids, and estrogen/testosterone depending on the pituitary hormone deficiency or deficiencies.

account. In two of the largest case series of ICPi-related hypophysitis for which the number of males and females treated with ICPi therapy for melanoma was reported, the incidence of hypophysitis was 15% in males compared with 4% in females in one study ($P = 0.02$; OR, 4.73; 95% CI, 1.27 to 30.79) (155) and 16% in males compared with 9% in females in the other study (154).

Pathophysiology of ICPi-related hypophysitis

Pathogenesis

The precise pathogenesis of ICPi-related hypophysitis remains unknown. *In vitro* studies and studies in murine models show potential roles for activation of both antibody-dependent cell-mediated cytotoxicity (ADCC) and the complement pathway in ipilimumab-related hypophysitis. Ipilimumab has been shown to activate ADCC (159, 160). As discussed above, Iwama *et al.* (141) created a murine model of anti-CTLA-4-related hypophysitis by administering repeated injections of an anti-CTLA-4 mAb into mice. Pituitary pathology showed infiltration with hematopoietic mononuclear cells, consisting predominantly of CD45+ lymphocytes. Additionally, mice receiving the anti-CTLA-4 antibody developed antibodies directed against the anterior pituitary that were not present prior to anti-CTLA-4 treatment, suggesting that anti-CTLA-4 injections can induce both cellular and humoral immune responses against the anterior pituitary. Further investigation demonstrated that CTLA-4 is expressed in both murine and human pituitary glands, predominantly in pituitary thyrotroph and lactotroph cells. Anti-CTLA-4 injections in mice led to a type 2 hypersensitivity reaction in which the classical complement pathway was activated, leading to deposition of complement on thyrotrophs and lactotrophs. Although direct evidence of binding of the anti-CTLA-4 antibody to the CTLA-4 antigen on pituitary cells was not shown, the findings provide insight into potential mechanisms of ICPi-related hypophysitis. Of note, in humans, ACTH deficiency is one of the most common clinical manifestations of ICPi-related hypophysitis; given this observation, it is unclear why corticotrophs were not affected in this mouse model. It is possible that pituitary responses to anti-CTLA-4 antibodies vary across different species. In addition, a type 2 hypersensitivity reaction may be only one of multiple pathophysiologic mechanisms that mediate anti-CTLA-4-induced hypophysitis.

Interestingly, the IgG subclass of specific ICPi agents may potentially play a role in differential risk of development of hypophysitis among different ICPi agents (141). Ipilimumab, durvalumab, atezolizumab, and avelumab are of the IgG1 subclass; tremelimumab (an anti-CTLA-4 mAb) is of the IgG2 subclass; and nivolumab and pembrolizumab are of the IgG4 subclass (Table 1). Each IgG subclass has different relative potency in activating ADCC and the classical complement pathway (161). IgG1 has relatively stronger effects on triggering ADCC compared with IgG2 and IgG4 subclasses and can activate the classical complement pathway. IgG2 has less potency than IgG1 both in activating ADCC and the classical complement pathway. IgG4 also has relatively less potency than IgG1 in activating ADCC and cannot activate the classical complement pathway. The fact that ipilimumab is IgG1-based and thus able to activate both ADCC and the classical complement pathway may potentially contribute to the higher incidence of hypophysitis due to ipilimumab compared with other ICPi therapy. PD-L1 has been found to be expressed in various human pituitary tumors (162). Whether PD-L1, PD-L2, and/or PD-1 are expressed in normal human pituitary tissue remains unclear. Of note, the Fc region of durvalumab and atezolizumab has been modified in such a way that neither of these agents induce either ADCC or complement-dependent cytotoxicity.

Iwama *et al.* (141) studied patients treated with ipilimumab with and without hypophysitis as an irAE and found that antipituitary antibodies were present in seven of seven patients who had developed ipilimumab-related hypophysitis and absent in 13 of 13 patients treated with ipilimumab who had not developed ipilimumab-related hypophysitis (141). These antipituitary antibodies had been negative in all of the patients at baseline. Further investigation showed that the antipituitary antibodies recognized predominantly thyrotroph cells in the pituitary; the antibodies also recognized corticotrophs and gonadotrophs in several patients. Whether antipituitary antibodies play a role in

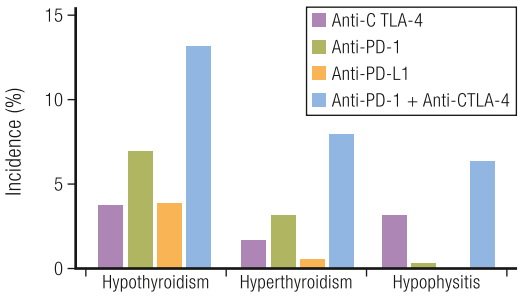


Figure 4. Incidence of thyroid dysfunction and hypophysitis induced by different ICPi regimens. The highest incidence of thyroid dysfunction is associated with combination therapy with anti-CTLA-4 and anti-PD-1 therapy. In monotherapy groups, the incidence of hypothyroidism and hyperthyroidism is higher with anti-PD-1 monotherapy than with anti-CTLA-4 or anti-PD-L1 monotherapy. On the other hand, the incidence of hypophysitis is higher with anti-CTLA-4 monotherapy than with anti-PD-1 or anti-PD-L1 monotherapy. With data from Barroso-Sousa R, Barry WT, Garrido-Castro AC, *et al.* Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol.* 2018;4(2):173–182. [© 2019 Illustration Presentation ENDOCRINE SOCIETY].

pathogenesis, prediction, or prognosis of ICPi-related hypophysitis remains unclear.

Because most CTLA-4 polymorphisms do not change the amino acid sequence of the CTLA-4 protein (Fig. 3), these polymorphisms would not be expected to alter the binding affinity of anti-CTLA-4 antibodies to CTLA-4. Rather, polymorphisms may alter the expression level of CTLA-4, and this in turn could impact the efficacy of CTLA-4 antibodies, making patients more or less prone to CTLA-4-blockade-induced hypophysitis. Other unknown mechanisms likely contribute to pathogenesis of ICPi-related hypophysitis.

Pathology

Pituitary pathology in ICPi-related hypophysitis has not been well-studied. To the best of our knowledge, no patient with ICPi-related hypophysitis has undergone a pituitary biopsy. The pathology in lymphocytic hypophysitis has been more thoroughly studied, with the major pathological feature being infiltration of the pituitary with lymphocytes. Both T-cells and B-cells can be seen in the pituitary on immunohistochemistry in patients with lymphocytic hypophysitis (149). Whether similar findings are present in ICPi-related hypophysitis remains to be determined.

Caturegli *et al.* (157) described the first autopsy examination of pituitary pathology in a patient with a history of ICPi-related hypophysitis. The patient was a 79-year-old woman who developed hypophysitis, with central adrenal insufficiency and central hypothyroidism, after receiving three doses of tremelimumab. An MRI scan confirmed an enlarged pituitary gland consistent with hypophysitis. She died ~15 months after her first dose of tremelimumab. Autopsy showed near complete destruction of her anterior pituitary gland due to extensive necrosis. Two isolated areas of the pituitary gland showed a few acini of endocrine cells, which were mainly somatotrophs; lactotrophs and corticotrophs were rare, and gonadotrophs and thyrotrophs were absent. Her posterior pituitary gland was normal.

Clinical, biochemical, and imaging manifestations of ICPi-related hypophysitis

Table 3 provides a summary of key clinical, biochemical, and imaging findings from four of the largest longitudinal cohorts that detailed findings from patients who developed ipilimumab-related hypophysitis.

Clinical manifestations

Symptoms of ICPi-related hypophysitis are typically nonspecific. Headache and fatigue are the most common presenting symptoms (155, 156, 163). Other symptoms may include nausea, decreased appetite, dizziness, decreased libido, cold intolerance, hot flashes, and weight loss. In contrast to other forms of autoimmune hypophysitis such as lymphocytic hypophysitis (157), symptoms due to mass effect (such as visual deficits due to impingement of the optic chiasm by the enlarged pituitary gland) are rare in ICPi-related hypophysitis, likely due to the mild degree of pituitary enlargement. Ipilimumab-related hypophysitis typically presents ~2 to 3 months after ipilimumab initiation (157) but has been reported as long as 19 months after ipilimumab initiation (156).

Biochemical findings

The diagnosis of ICPi-related hypophysitis is based on a combination of biochemical and radiographic findings. Biochemical evidence of deficiencies in one or more pituitary hormones is extremely common in ICPi-related hypophysitis. Central hypothyroidism, central adrenal insufficiency, and hypogonadotropic hypogonadism are the most common pituitary abnormalities in anti-CTLA-4-related hypophysitis, occurring in more than 80% of patients with this diagnosis (157). Biochemical findings are described below by hormonal axis.

Thyroid axis. Central hypothyroidism is one of the most common anterior pituitary hormone deficiencies in ICPi-related hypophysitis. Central hypothyroidism is characterized by a low or low-normal free T_4 in the setting of an inappropriately low or normal TSH (165). Faje *et al.* (155) noted a trend of declining TSH levels that preceded the diagnosis of ICPi-related hypophysitis and onset of symptoms. It is important to note that concomitant nonthyroidal illness syndrome (NTIS; also called euthyroid sick syndrome) can present with similar thyroid function tests (TFTs). NTIS is typified by a progressive decline in serum T_3; if the underlying illness does not improve, decreases in serum T_4 and TSH can be seen as well (166–168). The clinical context should be weighed carefully, and comparison with baseline TFTs prior to starting ICPi therapy can be helpful.

Adrenal axis. Central adrenal insufficiency is also common in ICPi-related hypophysitis. Importantly, morbidity due to ICPi-related hypophysitis is likely predominantly mediated by central adrenal insufficiency, which may be life-threatening if prompt treatment with corticosteroids is not initiated. Signs of adrenal crisis include hypotension, electrolyte imbalances (especially hyponatremia), and dehydration and require immediate treatment (169, 170). Hyponatremia in central adrenal insufficiency is mediated by increased secretion of antidiuretic hormone (ADH), resulting in water retention and a decrease in plasma sodium concentration. This increase in ADH secretion is caused by increased hypothalamic secretion of CRH, which stimulates ADH secretion (171, 172). Central adrenal insufficiency is characterized by a low or inappropriately normal ACTH in the setting of a low or low-normal cortisol. Of note, ACTH and cortisol levels vary based

Table 3. Summary of Longitudinal Case Cohorts of Ipilimumab-Related Hypophysitis

	Ryder *et al.* (156)	Faje *et al.* (155)	Albarel *et al.* (163)	Min *et al.* (154)	Total
Total number of patients studied	211	154	87–131[a]	187	639–683[a]
Number of patients diagnosed with hypophysitis	19/211 (9%)	17/154 (11%)	15/87–131[a] (11%–17%)	25/187 (13%)	76/639–683[a] (11%–12%)
Males and females diagnosed with hypophysitis	Males: 11/134 (8%)	Males: 15/99 (15%)	Males: 10[b]	Males: 19/118 (16%)	Males: 45/351[c] (13%)
	Females: 8/77 (10%)	Females: 2/55 (4%)	Females: 5[b]	Females: 6/69 (9%)	Females: 16/201[c] (8%)
Median time to diagnosis of hypophysitis after ICPi initiation	4 mo	8.4 wk	9.5 wk	9 wk	n/a
Number of patients with hypophysitis with radiographic pituitary enlargement	7/12 (75%)	17/17 (100%)	12/14 (86%)	15/25 (60%)	51/68 (75%)
Symptoms and signs					
Headache	6/19 (32%)	14/17 (82%)	13/15 (87%)	n/a	33/51 (65%)
Fatigue or weakness	13/19 (68%)	10/17 (59%)	11/15 (73%)	n/a	34/51 (67%)
Visual deficits	n/a	0/17 (0%)	0/15 (0%)	0/25 (0%)	0/57 (0%)
Hyponatremia	n/a	8/14 (57%)	n/a	14/25 (56%)	22/39 (56%)
Pituitary hormone dysfunction at diagnosis					
Adrenal	16/16 (100%)	7/14 (50%)	11/15 (73%)	22/25 (88%)	56/70 (80%)
Thyroid	11/18 (61%)	17/17 (100%)	13/15 (87%)	22/25 (88%)	63/75 (84%)
Gonadal	5/13 (38%)	15/15 (100%)	12/14 (86%)	15/20 (75%)	47/62 (76%)
GH (IGF-1)	n/a	1/6 (17%)	2/8 (25%)	3/7 (43%)	6/21 (29%)
Prolactin (elevated)	n/a	0/13[c] (0%)	1/9 (11%)	1/9 (11%)	2/31 (6%)
Prolactin (low)	n/a	12/13 (92%)	3/9 (33%)	4/9 (44%)	19/31 (61%)
DI	0/19 (0%)	0/17 (0%)	0/15 (0%)	0/25 (0%)	0/57 (0%)
Pituitary hormone dysfunction at most recent follow-up					
Adrenal	(3 recovered)[d]	14/17[e] (82%)	13/15 (87%)	22/25 (88%)	49/57 (86%)
Thyroid	(0 recovered)[d]	13/17[e] (76%)	2/15 (13%)	8/25 (32%)	23/57 (40%)
Gonadal	(2 recovered)[d]	13/15 (87%)	2/15 (13%)	8/25 (32%)	23/50 (46%)
Resolution of pituitary enlargement on follow-up imaging	n/a	17/17[f] (100%)	11/11 (100%)	11/11[g] (100%)	39/39 (100%)

Table includes data from Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. *Pituitary*. 2016;19(1):82–92 (164).

[a]In Albarel *et al.* (163), several patients were included in trials that were blinded at the time of publication; hence, the true number of patients who received ipilimumab ranged from 87 to 131.

[b]The number of males and females in the total cohort studied was not reported in Albarel *et al.* (163).

[c]Total numbers listed here are from Ryder *et al.* (156), Faje *et al.* (155), and Min *et al.* (154); Albarel *et al.* (163) was excluded from the total numbers as the number of males and females in the cohort studied were not reported.

[d]The number of patients who recovered pituitary function for the adrenal, thyroid, and gonadal axes was reported; the number of patients with pituitary hormone dysfunction at most recent follow-up was not explicitly detailed.

[e]Results were noted or updated in a subsequent article (164).

[f]In 7/7 patients who underwent repeat imaging within 40 d of the diagnosis of hypophysitis, resolution was observed on imaging.

[g]Four patients did not have repeat imaging studies before the end of the study. Median time to resolution was 15 wk (range, 2 to 27 wk). Of the 11 patients with resolution of pituitary enlargement, six had earlier MRI studies, at 3 to 8 wk after identification of pituitary enlargement, which did not show resolution of pituitary enlargement.

on diurnal patterns and need to be interpreted accordingly; typically, ACTH and cortisol levels peak in the early morning and thus early morning levels (*i.e.,* at 0800 hours) may be the most helpful (165, 169). In particular, an insufficient cortisol elevation in response to cosyntropin stimulation can help confirm the diagnosis of adrenal insufficiency (165, 169). A cosyntropin (ACTH) stimulation test can be helpful in the evaluation of adrenal insufficiency. Cortisol is tested at baseline (prior to cosyntropin administration) and 30 and/or 60 minutes after administration of 250 μg of IV cosyntropin. A peak cortisol level below 18 μg/dL at 30 or 60 minutes after cosyntropin administration is consistent with adrenal insufficiency (165). It is important to note two particular situations in which consideration of the clinical context is crucial in interpreting the results of cosyntropin stimulation testing. First, in central adrenal insufficiency of recent onset, a normal rise in cortisol can be seen in response to cosyntropin stimulation, because it takes time for the adrenal glands to atrophy in response to diminished ACTH secretion (173). Hence, a normal cosyntropin stimulation test cannot definitively exclude adrenal insufficiency. In such cases, the clinical context must be weighed to determine whether empiric glucocorticoid replacement is indicated, and close monitoring and repeat testing may be prudent. Second, in the context of concomitant synthetic corticosteroid therapy (such as in the treatment of irAEs due to ICPi therapy), a cosyntropin stimulation test may show an insufficient rise in cortisol. Exogenous corticosteroids can suppress CRH and ACTH and cause central adrenal insufficiency. If hypophysitis is suspected or confirmed in a patient already receiving synthetic corticosteroids and the patient fails cosyntropin stimulation testing, this reflects a diagnosis of adrenal insufficiency but does not differentiate the etiology (*i.e.*, corticosteroid use vs hypophysitis). These patients require continuation of glucocorticoid therapy until glucocorticoid doses can be tapered to physiologic doses. At that point, testing for functional recovery of the hypothalamic-pituitary-adrenal axis should be performed before attempting to stop glucocorticoids.

Gonadal axis. Hypogonadotropic hypogonadism is also common and manifests biochemically as low or inappropriately normal FSH and/or LH. In men, testosterone levels are low; as testosterone levels vary based on a diurnal pattern and peak in the morning, measurement of a morning total testosterone level (*i.e.,* between 0800 and 1000 hours) is recommended (174). In premenopausal women, estradiol levels are low in hypogonadotropic hypogonadism; in postmenopausal women, in whom FSH and LH are typically elevated compared with premenopausal women, inappropriately low FSH and LH suggest hypogonadotropic hypogonadism. Of note, FSH and LH are commonly transiently low in the setting of illness, and testing of the hypothalamic-pituitary-gonadal axis should be interpreted in the context of concurrent illness.

GH axis. The prevalence of GH deficiency in ICPi-related hypophysitis is unclear. This is likely due to two factors: (1) treatment of GH deficiency with GH replacement is contraindicated in the setting of active malignancy, and (2) confirmation of GH deficiency typically requires provocative testing with an insulin tolerance test, arginine-GH-releasing hormone stimulation test (not available in the United States), or glucagon stimulation test (175). IGF-1 levels may be low or within reference range (154, 155, 163); however, without provocative testing it is difficult to determine whether this represents true GH deficiency.

Prolactin. Hyperprolactinemia is uncommon in ICPi-related hypophysitis. Prolactin levels may be low. (Table 3) (154, 155, 163).

ADH. ADH is produced by hypothalamic neurons and stored in the posterior pituitary (neurohypophysis). ADH deficiency can result in DI, characterized by marked polyuria and production of dilute urine, which can result in hypernatremia if fluid intake is not maintained. DI appears to be extremely rare in ICPi-related hypophysitis and has only been reported in a few instances (176–179).

Radiographic features

Pituitary enlargement on radiographic imaging is a sensitive and specific indicator of ICPi-related hypophysitis after metastatic disease has been ruled out (155). Pituitary enlargement is generally mild to moderate, and thickening of the pituitary stalk may be seen (Fig. 5). Impingement of the optic chiasm is rare. Contrast enhancement may be homogeneous or heterogeneous. Pituitary enlargement may precede the clinical diagnosis of hypophysitis by several weeks (155). Based on this, we recommend that brain MRIs for patients being treated with ICPi therapy (particularly with ipilimumab) be compared with prior studies to monitor for changes in pituitary size that may herald impending anterior pituitary hormone dysfunction.

Pituitary enlargement resolves within weeks to months in nearly all cases of ICPi-related hypophysitis. Faje *et al.* (155) noted radiographic resolution of hypophysitis within 40 days of the diagnosis of ICPi-related hypophysitis in all seven patients who underwent repeat imaging within that timeframe; in one patient, pituitary enlargement resolved in 12 days (155). Min *et al.* 154) reported a longer median time to radiographic resolution of pituitary enlargement of 15 weeks (range, 2 to 27 weeks).

Importantly, a normal-appearing pituitary gland on imaging does not rule out hypophysitis, and management should be based on clinical and biochemical evaluation. Caturegli *et al.* (157) found that in 88 case reports of hypophysitis secondary to CTLA-4 blockade, MRI findings were normal in 20 cases (23%).

Given the transient nature of ICPi-related hypophysitis and the fact that radiographic pituitary enlargement may precede biochemical manifestations of hypopituitarism, it is possible that radiographic pituitary enlargement may resolve by the time that biochemical evidence of hypopituitarism is diagnosed.

Management of ICPi-related hypophysitis

Counseling on symptoms and signs of hypophysitis

Patients and their families should be counseled about the symptoms and signs of hypophysitis, as these may present between treatment visits and may require prompt management, particularly in cases of adrenal insufficiency.

Monitoring

Thyroid axis. We recommend that a TSH and free T4 be checked prior to ICPi initiation and at every treatment visit for at least the first five cycles of ICPi therapy (see section on ICPi-related thyroid dysfunction).

Adrenal axis. The package insert for ipilimumab recommends monitoring ACTH before the start of ipilimumab and before each dose (180). As described earlier, we recommend that ACTH be checked (1) simultaneously with cortisol to provide a more complete assessment of the hypothalamic-pituitary-adrenal axis, and (2) in the morning (*e.g.*, 0800 to 0900 hours) when ACTH and cortisol levels are generally at their peak. Of note, blood samples drawn for ACTH analysis should be transported on ice and processed promptly as temperature and/or time can lead to degradation and falsely low levels of ACTH (181–184). In our practice, we do not routinely check ACTH but given the morbidity of adrenal insufficiency and the nonspecific symptoms associated with adrenal insufficiency, we recommend a low threshold for testing a paired ACTH and cortisol for patients on ICPi therapy (especially ipilimumab-containing regimens) who present with symptoms or signs concerning for adrenal insufficiency. This is particularly true within the first few months after ipilimumab initiation, when the incidence of ipilimumab-induced hypophysitis appears to be greatest. It is important to keep in mind that ACTH levels that fall within the reference range do not definitively exclude central adrenal insufficiency.

Gonadal axis. In patients with hypophysitis or hypopituitarism, gonadotropin (FSH and LH) levels and sex hormone levels (estradiol in women or testosterone in men) should be assessed (165).

GH axis. Given that treatment of GH deficiency with GH replacement is contraindicated in the setting of active malignancy (175), there is limited utility in testing the GH axis in the setting of ICPi-related hypophysitis.

Prolactin. If hypogonadotropic hypogonadism is diagnosed, prolactin levels can be checked to rule out hyperprolactinemia, although hyperprolactinemia appears to be relatively rare in ICPi-related hypophysitis; more commonly, prolactin levels are low (Table 3) (154, 155, 163).

Hormone replacement

Thyroid axis. Levothyroxine should be initiated for treatment of central hypothyroidism. Importantly, in cases of concomitant adrenal insufficiency and hypothyroidism, glucocorticoid replacement should precede thyroid hormone replacement, as thyroid hormone replacement in the setting of untreated

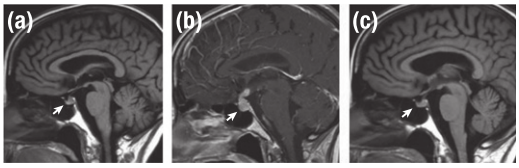


Figure 5. ICPi-related hypophysitis. Brain MRI showing development and resolution of ICPi-related hypophysitis in a 54-year-old woman with metastatic lung adenocarcinoma treated with nivolumab and a history of primary hypothyroidism on thyroid hormone replacement with levothyroxine. (a) Brain MRI, obtained 4 mo prior to nivolumab initiation, showed a normal-appearing pituitary gland (white arrow). Two wk after her third dose of nivolumab (3 mo after nivolumab initiation), she presented to oncology clinic with a 1-wk history of headache, nausea, anorexia, fatigue, generalized weakness, and lightheadedness. She was admitted to the hospital for further evaluation and management. Laboratory testing demonstrated new onset of hyponatremia (sodium 118 mmol/L; reference range, 135 to 145 mmol/L), low 0800 h cortisol (0.8 μg/dL; reference range, 6 to 24 μg/dL), low ACTH (<5.0 pg/mL; reference range, 10 to 60 pg/mL), low TSH (0.21 mIU/L; reference range, 0.50 to 5.00 mIU/L), and low-normal free T4 (1.0 ng/dL; reference range, 0.9 to 1.7 ng/dL) while on her baseline dose of levothyroxine. These laboratory findings were most consistent with central adrenal insufficiency and new onset of central hypothyroidism. Cosyntropin stimulation test demonstrated a suboptimal rise in cortisol from 0.8 to 10.3 μg/dL 60 min after administration of IV cosyntropin 250 μg, confirming adrenal insufficiency. (b) Brain MRI postgadolinium contrast, obtained the d after she presented to clinic, showed a bulky, diffusely enlarged, hyperenhancing pituitary gland (white arrow) with stalk thickening, consistent with nivolumab-induced hypophysitis. She was started on replacement dose hydrocortisone (30 mg total daily in divided doses), and her levothyroxine dose was increased, with normalization of her sodium within 24 h of her first dose of hydrocortisone. Interestingly, she developed DI on the fourth d of her hospitalization, with a 24-h urine output of 7.3 L, serum sodium of 148 mmol/L, urine osmolality of 123 mOsm/kg water (reference range, 390 to 1093 mOsm/kg water). She was started on desmopressin (DDAVP) with symptomatic control of her DI and normalization of her sodium. (c) Brain MRI, obtained 2 mo after her initial presentation with hypophysitis, showed resolution of pituitary enlargement (white arrow). She had partial resolution of her DI and was able to stop DDAVP 6 mo after it was diagnosed. Two y after her hypophysitis, her central adrenal insufficiency and hypothyroidism persist. [© 2019 Illustration Presentation ENDOCRINE SOCIETY].

adrenal insufficiency can worsen symptoms and potentially precipitate adrenal crisis (185–187). Also of note, in central hypothyroidism, unlike in primary hypothyroidism, TSH levels are unreliable, and levothyroxine should be titrated to a goal of the middle to upper half of the reference range for free T4 (166). We recommend initiating thyroid hormone replacement with levothyroxine at a dose of 0.8 μg/kg daily in young patients without a history of cardiovascular disease. Our rationale behind this starting dose is to reduce the risk of overreplacement of thyroid hormone, especially because (i) ICPi-related central hypothyroidism may be transient and may resolve spontaneously; (ii) the dose can be uptitrated as needed; and (iii) initiating levothyroxine at lower vs higher doses did not affect the rate of improvement of signs and symptoms of hypothyroidism or quality of life (188). We recommend repeating TSH and free T4 measurements 4 weeks after levothyroxine initiation and titrating levothyroxine further based on these results; in many patients, full weight-based dosing of ~1.6 to 1.8 μg/kg/d may be needed (165, 166). For patients with known coronary heart disease, we recommend initiating levothyroxine at a lower dose [*e.g.,* 12.5 to 25 μg by mouth (PO) daily], repeating TSH and free T4 measurements 4 weeks after levothyroxine initiation, and titrating the dose accordingly based on free T4 levels (166). Also, for older patients (such as those over 65 years), it may be reasonable to start levothyroxine at a lower dose and monitor TFTs more frequently, given that older patients are more susceptible to adverse effects of thyroid hormone overreplacement such as atrial fibrillation and osteoporotic fractures (166). Although thyroid hormone replacement in central hypothyroidism should be based on free T4 levels, as highlighted above, we continue to monitor TSH in cases of central hypothyroidism because development of an elevated TSH after a diagnosis of central hypothyroidism may signal recovery of the thyrotrophs in the pituitary and development of primary hypothyroidism or could signal the recovery phase of NTIS (167, 168).

Adrenal axis. High-dose corticosteroids should be started promptly for patients with adrenal crisis and can be considered in patients with substantial pituitary enlargement that impinges on the optic chiasm. For patients with evidence of adrenal insufficiency who are not critically ill, replacement doses of corticosteroids should be initiated (for example, with 15 to 20 mg of hydrocortisone PO daily in divided doses) (165). In patients already being treated with systemic corticosteroids (*e.g.,* for the management of nonendocrine-related irAEs due to ICPi therapy), assessment of the endogenous hypothalamic-pituitary-adrenal axis can be challenging because systemic corticosteroids can directly suppress ACTH and cause central adrenal insufficiency. Typically, in such cases, systemic corticosteroids should be tapered to physiologic doses as tolerated/indicated, at which point testing for functional recovery of the endogenous hypothalamic-pituitary-adrenal axis should be performed before attempting to discontinue glucocorticoids. In agreement with the Endocrine Society guidelines on central adrenal insufficiency, we recommend that health care providers counsel all patients with adrenal insufficiency regarding sick day rules and stress-dose and emergency corticosteroid administration, instruct them to obtain medical alert gear (such as a bracelet or necklace) regarding adrenal insufficiency, and prescribe a kit with injectable high-dose corticosteroid for emergency use (165).

Gonadal axis. Sex hormone replacement (testosterone in men and estradiol in women) may be considered for men and for premenopausal women with ICPi-related hypogonadotropic hypogonadism if not contraindicated (165, 174). For men, testosterone therapy is not recommended in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level > 4 ng/mL, a prostate-specific antigen level > 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia (165, 174). In men older than 65 years who have symptoms or clinical findings suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, testosterone therapy may be offered on an individualized basis after discussion of risks and benefits (174). For women, the risks and benefits of estrogen therapy should be weighed on an individual basis, taking into account symptoms, age, menopausal status, and personal and family history, as there are no commonly recognized lists of absolute or relative contraindications to estrogen therapy in professional society guidelines. Generally, estrogen therapy should not be used in women with a history of breast cancer, endometrial cancer, or other estrogen-dependent neoplasia; a history of venous or arterial thromboembolism including coronary heart disease, stroke, and transient ischemic attack; thrombophilia; unexplained vaginal bleeding; substantial liver impairment; or pregnancy (189, 190). Caution should be used with estrogen therapy in women with DM, asthma, gallbladder disease, hypertriglyceridemia, migraine with aura, hypoparathyroidism, hepatic hemangioma, systemic lupus erythematosus, epilepsy, benign meningioma, porphyria cutanea tarda, intermediate or high risk of breast cancer, and high risk of heart disease (189, 190).

Hyponatremia, if present, typically resolves after appropriate corticosteroid and thyroid hormone replacement. If hyponatremia persists despite adequate

corticosteroid and thyroid hormone replacement, evaluation for other causes should be considered, such as inappropriate ectopic secretion of ADH from malignant cells, which can be seen in small cell lung cancers, head and neck cancers, and more rarely other malignancies (191–194).

Prognosis for pituitary recovery

Recovery from ICPi-related central adrenal insufficiency appears to be rare (155, 156, 195). Among patients who developed ICPi-related central adrenal insufficiency, adrenal insufficiency was persistent at last follow-up in 22/22 patients (154), 13/13 patients (163), and 10/10 patients (196).

Recovery from central hypothyroidism appears to be fairly common and occurred in 14/22 patients in a median of 10.5 weeks (range, 1 to 44 weeks) (154), 11/13 patients (163), and 0/10 patients (196). Recovery from central hypogonadism appears also to be fairly common and occurred in 7/15 patients in a median of 15 weeks (range, 2 to 92 weeks) (154), 10/12 patients (163), and 3/9 patients (196).

Of note, variations in the reported rates of pituitary hormone recovery may be the result of differences in follow-up and in strategies for weaning or testing patients off of hormone replacement.

Utility of high-dose corticosteroids in ICPi-related hypophysitis

In the ipilimumab package insert (180) and in the literature (197), high-dose corticosteroids are recommended for the treatment of ipilimumab-related hypophysitis. However, convincing data to support this approach are lacking. Min *et al.* (154) studied outcomes in patients with ICPi-related hypophysitis who did or did not receive high-dose corticosteroids and found that higher doses of corticosteroids did not appear to improve the frequency or time to resolution of recovery of pituitary function or affect overall survival (OS). In that study, replacement doses of corticosteroids were sufficient to substantially improve headaches and fatigue in patients with ICPi-related hypophysitis, without the need for high-dose corticosteroids. Given these findings, and in the absence of systematic studies comparing the outcomes of ICPi-related hypophysitis with and without high-dose corticosteroids, we recommend that high-dose corticosteroids be reserved for patients with ICPi-related hypophysitis who develop severe hyponatremia or substantial mass effect from pituitary enlargement (*e.g.,* impingement of the optic chiasm), or in the setting of critical illness.

ICPi continuation in the setting of hypophysitis

ICPi therapy may be continued or resumed in many cases of ICPi-related hypophysitis. The package insert for ipilimumab (180), for example, recommends withholding ipilimumab in the event of symptomatic endocrinopathy due to ipilimumab and resuming it in patients with complete or partial resolution of adverse reactions (grade 0 to 1) and who are receiving less than 7.5 mg of prednisone or its equivalent daily; for patients with symptomatic reactions lasting 6 weeks or longer with an inability to reduce corticosteroid dosing to 7.5 mg of prednisone or its equivalent daily, permanent discontinuation of ipilimumab is recommended as per the package insert. The dose cutoff of 7.5 mg of prednisone daily or its equivalent specified on the ipilimumab package insert is presumably because this is considered close to (in fact, slightly more than) physiologic replacement of glucocorticoids; the most recent Endocrine Society guidelines for glucocorticoid replacement in the setting of central or PAI estimate daily physiologic replacement of glucocorticoids to be the equivalent of hydrocortisone 15 to 25 mg/d (prednisone 3.75 to 6.25 mg/d) (165, 198). Min *et al.* (154) found that in patients with ipilimumab-related hypophysitis and associated deficiencies in one or more pituitary hormone axes, discontinuation of ipilimumab did not appear to affect the outcome or resolution of hypophysitis or hypophysitis-related hormonal deficiencies compared with patients in whom ipilimumab therapy was continued, and that resolution of pituitary hormone axes occurred in a subset of patients who were continued on ipilimumab therapy.

ICPi-Related Thyroid Dysfunction

"ICPi-related thyroid dysfunction most commonly presents as a painless thyroiditis that develops within weeks to months of ICPi initiation."

Introduction

Thyroid dysfunction is one of the most common endocrine-related irAEs associated with ICPi therapy (Box 6) (3, 199, 200). In clinical trials, ICPi-related thyroid dysfunction has been variously described as hyperthyroidism, hypothyroidism, and/or thyroiditis because it may present as overt or subclinical hypothyroidism or thyrotoxicosis. Several case series have shown that ICPi-related thyroid dysfunction appears to be due to destructive thyroiditis (200–210). Thyroid dysfunction appears to be more common with anti-PD-1 treatment and combination ipilimumab-nivolumab treatment than with anti-CTLA-4 monotherapy or anti-PD-L1 monotherapy (3). The findings from three of the largest studies of ICPi-related thyroid dysfunction are summarized in Table 4.

Incidence and epidemiology of ICPi-related primary thyroid dysfunction

Hypothyroidism

The incidence of hypothyroidism due to ICPi-induced primary thyroid dysfunction varied among different studies and ICPi therapies. A meta-analysis of 38 randomized controlled trials (RCTs) of anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapy found 472 cases of

BOX 6. Key points regarding ICPi-related thyroid dysfunction

- ICPi-related thyroid dysfunction, typically due to a destructive thyroiditis, is the one of the most common ICPi-related endocrinopathies.
- The spectrum of ICPi-related thyroid dysfunction includes overt thyrotoxicosis, subclinical thyrotoxicosis, subclinical hypothyroidism, and overt hypothyroidism.
- ICPi-related thyroid dysfunction often occurs within weeks to months after ICPi initiation.
- Hypothyroidism is the most common ICPi-related thyroid dysfunction.
- ICPi-related hypothyroidism may be preceded by a transient thyrotoxic phase which, if present, is typically mild or asymptomatic and lasts a few weeks before rapidly resolving to euthyroidism or hypothyroidism.
- ICPi-related thyroid dysfunction may be transient or permanent. Hypothyroidism may require long-term thyroid hormone replacement with levothyroxine.
- It is important that hypothyroidism, if present, be differentiated between primary and secondary (central) hypothyroidism, because if secondary hypothyroidism is present, the differential diagnosis of hypophysitis should be considered and assessed.
- Thyrotoxicosis, if present, is typically mild and self-limited. The mainstay of thyrotoxicosis is supportive care. Beta-blockers can be used as needed for symptom management of thyrotoxicosis. Corticosteroids and antithyroid drugs (thioamides) are rarely needed.
- Most ICPi-related thyroid dysfunction is mild and does not require interruption of ICPi therapy.
- Given the prevalence of ICPi-related thyroid dysfunction and the possibility of rapid evolution of overt/subclinical thyrotoxicosis or subclinical hypothyroidism to overt hypothyroidism, close monitoring of TFTs is recommended for patients receiving ICPi therapy.

hypothyroidism among 7551 patients (3). In the study, a mixed-effects model estimated the overall incidence of hypothyroidism with ICPi therapy to be 6.6% (95% CI, 5.5% to 7.8%). The predicted incidence of hyperthyroidism varied depending on the ICPi regimen (95% CI in parentheses): anti-CTLA-4 agents 3.8% (1.9% to 7.8%), anti-PD-L1 agents 3.9% (1.7% to 8.4%), anti-PD-1 agents 7.0% (3.9% to 12.3%), and combination ipilimumab-nivolumab 13.2% (6.9% to 23.8%) (Fig. 4). Patients who received anti-PD-1 agents (OR, 1.89; 95% CI, 1.17 to 3.05, adjusted $P = 0.03$) and those who were treated with combination ipilimumab-nivolumab (OR, 3.81; 95% CI, 2.10 to 6.91, unadjusted $P < 0.001$) were significantly more likely to experience hypothyroidism than those treated with ipilimumab monotherapy.

Hyperthyroidism

The reported incidence of hyperthyroidism due to ICPi-induced primary thyroid dysfunction is lower than that of hypothyroidism. As hyperthyroidism typically occurs earlier than hypothyroidism in ICPi-induced primary thyroid dysfunction and the hyperthyroid phase typically evolves to hypothyroidism (as will be discussed in detail later), many cases of hyperthyroidism may be missed in clinical studies. A meta-analysis of 37 RCTs of anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapy found 194 cases of hyperthyroidism among 7531 patients (3). In that study, a mixed-effects model estimated the overall incidence of hyperthyroidism with ICPi therapy to be 2.9% (95% CI, 2.4% to 3.7%). The predicted incidence of hyperthyroidism varied depending on the ICPi regimen (95% prediction interval in parentheses): anti-PD-L1 agents 0.6% (0.2% to 1.8%), anti-CTLA-4 agents 1.7% (0.8% to 3.8%), anti-PD-1 agents 3.2% (1.7% to 5.7%), and combination ipilimumab-nivolumab treatment 8.0% (4.1% to 15.3%) (Fig. 4). Patients who received combination ipilimumab-nivolumab treatment were significantly more likely to experience hyperthyroidism than those treated with ipilimumab monotherapy (OR, 4.27; 95% CI, 2.05 to 8.90, $P = 0.001$). In contrast, the increased incidence in patients who received anti-PD-1 agents did not reach statistical significance compared with patients who received ipilimumab monotherapy after correcting for multiple comparisons (OR, 1.89; 95% CI, 1.02 to 3.52, adjusted $P = 0.13$). Patients who received anti-PD-1 agents were significantly more likely to experience hyperthyroidism than those treated with anti-PD-L1 agents (OR, 5.36; 95% CI, 2.04 to 14.08, adjusted $P = 0.002$).

In the largest single-center study of ICPi-related thyroid dysfunction, Morganstein *et al.* (200) confirmed relatively high rates of thyroid dysfunction (including both overt and subclinical hypothyroidism and thyrotoxicosis) in patients receiving ICPi therapy and found the highest rates among patients receiving combination ipilimumab-nivolumab therapy. Of 190 consecutive patients included in the study, 56 (30%) developed thyroid dysfunction, with rates lowest among those on ipilimumab monotherapy (29/126 patients, or 23%), intermediate among those on anti-PD-1 monotherapy (18/46 patients, or 39%), and highest among those on combination ipilimumab-nivolumab therapy (9/18, or 50%). Patients with treatment-induced hypopituitarism, with abnormal thyroid function prior to initiating ICPi therapy, or without baseline TFTs available were excluded from the study.

Natural history of ICPi-related primary thyroid dysfunction

ICPi-related hypothyroidism and thyrotoxicosis

ICPi-related thyroid dysfunction most commonly presents as a painless thyroiditis that develops within weeks to months of ICPi initiation. Biochemically, TFTs may show extreme laboratory values such as free T4 levels above the assay limit in thyrotoxicosis and below the assay limit in hypothyroidism. Clinically, most patients present with mild symptoms even in the setting of such extreme laboratory values. It is possible that the patients could remain clinically euthyroid transiently during the acute dramatic changes in thyroid hormone levels. Without proper management, severe symptoms of thyroid dysfunction could potentially arise. Overt or subclinical thyrotoxicosis may be the initial presentation, which typically spontaneously resolves to euthyroidism and often evolves into hypothyroidism within the course of several weeks to months. In the remainder of cases, overt or subclinical hypothyroidism is the initial presentation, which may be transient or permanent. Time from first ICPi dose to detection of thyroid dysfunction is often relatively short (on the order of several weeks) and can occur after a single dose of ICPi therapy (201). Case series of ICPi-related thyroid dysfunction have reported that the median time from initiation of the ICPi being studied to detection of thyroid dysfunction ranged from 18 to 123 days (75, 196, 200, 201, 204–210). However, the onset of ICPi-related thyroid dysfunction has been reported to occur as early as 7 days after ICPi initiation or as late as 3 years after ICPi initiation (156, 201).

Lee *et al.* (201) retrospectively studied 45 patients with ICPi-related thyroid dysfunction at a single institution, focusing on the natural history of ICPi-related thyroid dysfunction. These patients were treated with anti-PD-1 monotherapy (nivolumab or pembrolizumab) or combination ipilimumab-nivolumab therapy. Thyrotoxicosis was the initial presentation in 78% (35/45) of patients, whereas hypothyroidism was the initial presentation in the remaining 22% (10/45) of patients. Of the 35 patients who presented with thyrotoxicosis, 80% (28/35) subsequently developed hypothyroidism. For patients with thyrotoxicosis, the median time to onset was 21 days (range, 7 to 64 days) in the combination ipilimumab-nivolumab group and 47 days (range, 14 to 447 days) in the anti-PD-1 monotherapy group. For patients with hypothyroidism, the median time to onset was longer than that for thyrotoxicosis: 63 days (range, 24 to 141 days) in the combination ipilimumab-nivolumab group and 70 days (range, 27 to 475 days) in the anti-PD-1 monotherapy group. Four studies have examined the time from onset of ICPi-related thyrotoxicosis to resolution of thyrotoxicosis or evolution to hypothyroidism; all found the median time course for this was on the order of ~4 to 7 weeks (75, 196, 201, 207). A shorter time to onset of thyrotoxicosis, longer time to onset of hypothyroidism, and conversion of thyrotoxicosis to hypothyroidism support destructive thyroiditis as the underlying process in ICPi-related thyroid dysfunction.

Numerous other studies have found a similar common pattern of transient overt or subclinical thyrotoxicosis followed by euthyroidism or hypothyroidism in patients receiving ICPi therapy (75, 156, 196, 200, 204–208, 210, 211). De Filette *et al.* (204) studied 99 patients with melanoma treated with pembrolizumab and found that 17 (17.2%) developed thyroid dysfunction during the study period. Twelve patients (12.1% of total patients studied) developed thyrotoxicosis (3 of grade 1, 8 of grade 2, and 1 of grade 3); in 9 of these 12, initial thyrotoxicosis later progressed to hypothyroidism. Six patients (6.1% of total patients studied) developed isolated hypothyroidism. Of the 15 total patients who developed hypothyroidism, 3 were of grade 1 and 12 were of grade 2. Of note, of the 99 patients studied, 76 (76.8%) had received prior treatment with ipilimumab; of the 17 patients who developed thyroid dysfunction, 15 (88.2%) had received prior treatment with ipilimumab.

Many patients who develop overt hypothyroidism as a result of ICPi therapy will require levothyroxine replacement. In patients who developed overt hypothyroidism, levothyroxine was initiated in 12/12 patients (196), 10/15 patients (204), 10/10 patients (208), 8/10 patients (211), 7/10 patients (200), 6/6 patients (209), and 3/5 patients (212).

ICPi-related Graves disease

As emphasized earlier, the vast majority of ICPi-related thyrotoxicosis is transient and is likely caused by a destructive thyroiditis leading to release of preformed thyroid hormone. ICPi-related Graves disease with persistent stimulation of endogenous thyroid hormone production appears to be extremely rare but has been reported. Specifically, two cases of Graves disease have been reported in patients being treated with anti-CTLA-4 therapy. Azmat *et al.* (213) described a case of ipilimumab-related Graves disease in a 67-year-old man with metastatic melanoma treated with ipilimumab. After the second dose of ipilimumab, the patient developed clinical and biochemical hyperthyroidism, with a suppressed TSH, elevated free T3, elevated free T4, and elevated thyroid-stimulating immunoglobulin (TSI). An I-123 scan showed diffuse homogeneous thyroid uptake that was elevated at 6 and 24 hours, consistent with Graves disease. Antithyroid drug therapy with methimazole was started with restoration of normal free T3 and free T4 levels, and ipilimumab was able to be restarted. The patient later underwent a left neck dissection for residual metastatic melanoma along with total thyroidectomy; thyroid pathology revealed nodular and papillary hyperplasia of the thyroid consistent with

Table 4. Summary of Findings From Three of the Largest Studies of ICPi-Related Thyroid Dysfunction

Study	Morganstein *et al.* (200)	Lee *et al.* (201)	Scott *et al.* (196)
Total number of patients treated with ICPi therapy	190	n/a[a]	177
ICPi therapy			
Ipilimumab monotherapy	126/190 (66%)	0/45 (0%)	15/177 (8%)
Nivolumab or pembrolizumab monotherapy	46/190 (24%)	18/45 (40%)	103/177 (58%)
Combination ipilimumab-anti-PD-1 (nivolumab or pembrolizumab)	18/190 (9%)	27/45 (60%)	59/177 (33%)
Malignancy	Melanoma	Melanoma (64%), breast cancer (11%); remainder were ovarian cancer, bladder cancer, leiomyosarcoma, esophageal cancer, gastric cancer, RCC, anal cancer, brain GBM	Melanoma
Exclusions	Patients with hypopituitarism, with abnormal baseline TFTs, or without baseline TFTs available.	n/a	Patients who received sequential ipilimumab and then anti-PD-1 therapy (or *vice versa*).
Of total patients treated with ICPi therapy, patients who developed any ICPi-related thyroid dysfunction	56/190 (29%)	n/a[a]	24/177 (14%)
Ipilimumab monotherapy	29/126 (23%)	n/a[a]	2/15 (13%)
Nivolumab or pembrolizumab monotherapy	18/46 (39%)	n/a[a]	9/103 (9%)
Combination ipilimumab-anti-PD-1 (nivolumab or pembrolizumab)	9/18 (50%)	n/a[a]	13/59 (22%)
Thyroid dysfunction reported	Of the 56 patients who developed thyroid dysfunction, patients who developed specific types of thyroid dysfunction:	Of the 45 patients who developed thyroid dysfunction, patients who presented with specific types of thyroid dysfunction at initial presentation:	Of the 24 patients who developed thyroid dysfunction, 21 (88%) were frankly or subclinically hyperthyroid at diagnosis. This evolved to the following:
	- Primary hypothyroidism: 11/56 (20%).	- Hypothyroidism as the initial presentation of thyroid dysfunction: 10/45 (22%).	- Hypothyroidism: 9
	- Subclinical hypothyroidism: 15/56 (27%).	- Thyrotoxicosis as the initial presentation of thyroid dysfunction: 35/45 (78%). 28/35 (80%) subsequently developed hypothyroidism.	- Euthyroidism: 9
	- Subclinical hyperthyroidism: 30/56 (54%).		- Subclinical hyperthyroidism: 2
			- Frank hyperthyroidism: 1 (but the follow-up time for this patient was only 12 d).

(*Continued*)

Table 4. *Continued*

Study	Morganstein *et al.* (200)	Lee *et al.* (201)	Scott *et al.* (196)
Timeframes for ipilimumab-related thyroid dysfunction	Median time from first ICPi dose to first abnormal TSH in patients who developed primary hypothyroidism (1/126): 63 d.	n/a	Median time from first ICPi dose to thyroid dysfunction: 123 ± 122 d
	Median time from first ICPi dose to first abnormal TSH in patients who developed subclinical hypothyroidism (8/126): 65 d (range, 26–90 d).		
	Median time from first ICPi dose to first abnormal TSH in patients who developed subclinical hyperthyroidism: 50 d (range, 36–111 d).		
Timeframes for nivolumab- or pembrolizumab-related thyroid dysfunction	Median time from first ICPi dose to first abnormal TSH in patients who developed primary hypothyroidism (6/46 patients): 32 d (range, 25–57 d). Median time from first ICPi dose to peak TSH was 81 d (range, 58–107 d).	Median time from first ICPi dose to onset of thyrotoxicosis: 47 d (range, 14–447 d).	Median time from first ICPi dose to thyroid dysfunction: 65 ± 190 d
	Median time from first ICPi dose to first abnormal TSH in patients who developed subclinical hypothyroidism (6/46 patients): 66 d (range, 38–74 d).	Median time from onset of thyrotoxicosis to hypothyroidism (for those on nivolumab or pembrolizumab monotherapy to hypothyroidism): 42 d (range, 21–169 d).	Median time to resolution of thyroid dysfunction (in the nine patients whose thyroid dysfunction resolved): 33 ± 77 d.
	Median time from first ICPi dose to first abnormal TSH in patients who developed subclinical hyperthyroidism (6/46 patients): 57 d (range, 25–127 d). Median time from first ICPi dose to nadir TSH was 64 d (range, 28–197 d).	Median time from first ICPi dose to hypothyroidism: 70 d (range, 27–475 d).	
Timeframes for combination ipilimumab+anti-PD-1 (nivolumab or pembrolizumab)-related thyroid dysfunction	n/a	Median time from first ICPi dose to thyrotoxicosis: 21 d (7–64 d).	Median time from first dose of combination ICPi therapy to thyroid dysfunction: 30 ± 113 d
		Median time from onset of thyrotoxicosis to hypothyroidism (for those on combination ipilimumab-nivolumab therapy): 42 d (range, 17–77 d).	Median time to resolution of thyroid dysfunction (in the nine patients whose thyroid dysfunction resolved): 91 ± 108 d
		Median time from first ICPi dose to hypothyroidism: 63 d (range, 24–141 d).	
TPO Ab testing (patients with positive TPO Ab/total number of patients who both developed ICPi-related thyroid dysfunction and had TPO Ab measured)[b]	4/5 (80%)	6/11 (54%)	5/7 (71%)
Thyroid disorder treatment and ICPi management	Of 10 total patients who developed hypothyroidism, six needed levothyroxine.	No patient recovered from hypothyroidism during the study period.	Twelve patients developed hypothyroidism and required thyroid replacement, including nine of those who initially presented with hyperthyroidism.

Abbreviations: GBM, glioblastoma multiforme; RCC, renal cell carcinoma.
[a]Lee *et al.* (201) studied only patients who developed ICPi-related thyroid dysfunction and did not study patients who were treated with ICPi therapy but did not develop thyroid dysfunction.
[b]TPO Ab levels were not checked in all patients in Morganstein *et al.* (200) and Lee *et al.* (201).

Graves disease. Gan *et al.* (214) described a case of Graves disease in a 55-year-old man with metastatic melanoma treated with 8 years of tremelimumab therapy. The patient reported several months of unintentional weight loss and was found to have a suppressed TSH, elevated free T3, elevated free T4, and elevated antithyroperoxidase antibody (TPO Ab) levels and antithyrotropin receptor antibody (TRAb) levels that persisted for several months. He was diagnosed with Graves disease and treated with antithyroid drug therapy with carbimazole with simultaneous thyroid hormone replacement with levothyroxine ("block and replace therapy"), which was withdrawn after 12 months. He remained euthyroid thereafter and was able to restart tremelimumab treatment. In addition to Graves hyperthyroidism, we have reported a patient with ipilimumab-related Graves ophthalmopathy (215). She was euthyroid at initial presentation but developed hyperthyroidism 4 years after ipilimumab treatment.

Pathophysiology of ICPi-related primary thyroid dysfunction

As previously discussed earlier, *CTLA-4* is a major susceptibility gene for AITD, including Graves disease and Hashimoto thyroiditis. Whether polymorphisms in these genes may play a role in susceptibility to ICPi-related thyroid dysfunction is unclear.

Two studies used flow cytometric analysis to examine immune cell populations in patients with ICPi-related thyroid dysfunction. Delivanis *et al.* (207) performed flow cytometric analysis in three groups: healthy volunteers, patients with autoimmune thyroiditis, and patients with pembrolizumab-induced thyroiditis. More circulating CD56+CD16+ natural killer cells and an elevated HLA DR surface expression in the inflammatory intermediate CD14+CD16+ monocytes were observed in patients who developed pembrolizumab-related thyroiditis. The same study also compared PD-1 levels on peripheral T-cells in the three groups. PD-1 levels were not detectable on the surface of T-cells from patients with pembrolizumab-induced thyroiditis; in contrast, PD-1 expression on T-cells were similar between healthy volunteers and patients with autoimmune thyroiditis. This supports the hypothesis that immune-mediated thyroid dysfunction in pembrolizumab-induced thyroiditis may differ from that in autoimmune thyroiditis.

Torimoto *et al.* (216) performed flow cytometric analysis of peripheral blood lymphocytes in a patient who developed nivolumab-related hypothyroidism. Analysis of blood samples at baseline and 2 weeks after nivolumab showed a marked increase in the proportion of follicular helper T (Tfh) cells, from 0.9% at baseline to 3.1% 2 weeks after nivolumab, followed by a decrease to 1.2% at 4 months after treatment. At baseline, the patient was euthyroid but was positive for TPO Ab and anti-TgAb. After nivolumab, titers of both antibodies increased and marked hypothyroidism requiring long-term levothyroxine developed, along with new ultrasonographic evidence of thyroid atrophy and hypoechogenicity. Tfh cells express PD-1 and play a role in B-cell maturation and activation and in antibody production. Torimoto *et al.* (216) hypothesized that anti-PD-1 treatment led to suppression of PD-1/PD-L1 inhibitory signals in Tfh cells, which may have enhanced Tfh cell proliferation and contributed to development of hypothyroidism. Corroborating this hypothesis, increased percentages of circulating Tfh cells were found in patients with AITD, which correlated with higher serum concentrations of TPO Ab, and TgAb, and TRAb in patients with Graves disease and Hashimoto thyroiditis (217).

Thyroid autoantibodies as potential biomarkers for ICPi-related primary thyroid dysfunction

TPO Ab and TgAb

Studies have found that the prevalence of elevated titers of TPO Ab and/or TgAb in the general population ranges from 10.4% to 18.8%, with a twofold or higher prevalence in women compared with men (218–222). TPO Ab and TgAb have been found to be elevated in many cases of ICPi-related thyroid dysfunction (75, 196, 200, 201, 204–207, 209–212). Whether thyroid autoantibodies play a causal role in the pathogenesis of ICPi-related thyroid dysfunction and whether elevated thyroid autoantibody levels at baseline increase the risk for development of ICPi-related thyroid dysfunction remain unclear. Many patients who develop ICPi-related thyroid dysfunction do not have elevated titers of thyroid autoantibodies at the time of abnormal TFTs, suggesting TPO Ab and TgAb are not necessary for the development of ICPi-related thyroid dysfunction. It is possible that either the pathogenesis of ICPi-related thyroid dysfunction may not be due to thyroid autoantibodies or that other thyroid autoantibodies that are not being measured may be contributing to the pathogenesis. TPO Ab and TgAb may be present at baseline prior to or may develop after ICPi initiation (204, 205, 207, 208, 212). The development of elevated thyroid autoantibody levels after ICPi initiation does not guarantee the development of overt thyroid dysfunction (208). It is possible, for example, that the development of elevated thyroid autoantibody levels after ICPi initiation may be the result of a humoral response to the exposure of thyroid antigens caused by a destructive thyroiditis (156).

Elevated baseline TPO Ab and TgAb levels may be a risk factor for ICPi-related thyroid dysfunction, although more research is needed to confirm this. Maekura *et al.* (212) studied the utility of baseline TPO Ab and TgAb levels in predicting the development of nivolumab-induced hypothyroidism. Baseline TPO Ab and TgAb levels were measured in 53 patients

treated with nivolumab for nonsmall cell lung cancer (NSCLC). Of nine patients who had positive TPO Ab at baseline, 4/9 (44%) went on to develop ICPi-related hypothyroidism; of 44 patients who had negative TPO Ab at baseline, 1/44 (2%) went on to develop ICPi-related hypothyroidism. For TgAb, of nine patients who had positive TgAb at baseline, 5/9 (56%) went on to develop ICPi-related hypothyroidism; of 44 patients who had negative TgAb at baseline, 0/44 went on to develop ICPi-related hypothyroidism.

Osorio *et al.* (208) measured TPO Ab and TgAb levels at baseline and during treatment with pembrolizumab (208). These levels were measured before cycle 1, before cycle 2, and every other cycle thereafter in 48 patients treated with pembrolizumab for melanoma. Thyroid dysfunction was defined as at least two consecutive abnormal TSH levels, ultimately requiring treatment. Eleven of 48 patients studied (23%) had positive TPO Ab and/or TgAb, four of whom had positive antibody levels present at baseline and seven of whom developed positive thyroid autoantibody levels during pembrolizumab treatment. TPO Ab and/or TgAb was positive in 8/10 patients who developed thyroid dysfunction vs 3/38 patients who did not (80% vs 8%, $P < 0.0001$). This study suggests that the development of positive thyroid autoantibodies after the initiation of ICPi therapy is associated with higher risks for ICPi-induced thyroid dysfunction. However, because TSH and free T4 are routinely checked as part of monitoring with ICPi therapy, regularly assessing posttreatment thyroid autoantibody levels in patients being treated with ICPi therapy would likely not facilitate the diagnosis of ICPi-related thyroid dysfunction, while increasing costs.

TRAb

TRAb, including TSI and thyrotropin binding inhibitory immunoglobulin, have been measured in several case studies of ICPi-related thyroid dysfunction and have been negative in the vast majority of patients studied (75, 201, 204, 206, 207, 209–211). A single case series found a relatively high prevalence of elevated TSI [5/8 patients (63%) at time of initial thyroid dysfunction]; of note, the TSI elevations were mild, and none of these patients remained hyperthyroid (211). The findings raise the possibility of coexistence of destructive thyroiditis with Graves disease in some patients with ICPi-related thyroid dysfunction. Loss of thyroid function from destructive thyroiditis may have abolished the stimulatory effect of TSI on the thyroid.

Clinical and biochemical manifestations of ICPi-related primary thyroid dysfunction

Thyrotoxicosis

The symptoms of ICPi-related thyrotoxicosis are usually mild and nonspecific. Fatigue, weight loss, and palpitations are the most common symptoms reported by patients who develop ICPi-related thyrotoxicosis (201, 209). Additional clinical manifestations of thyrotoxicosis include heat intolerance, tremulousness, tremor, anxiety, and increased frequency of bowel movements (hyperdefecation). Physical examination may reveal tachycardia, warm smooth skin, lid lag, and brisk deep tendon reflexes. Atrial fibrillation may be seen, especially in older patients. Most cases of ICPi-related thyrotoxicosis are mild to moderate (*i.e.,* grade 1 and 2); in a meta-analysis of 37 RCTs of comprising a total of 7531 patients treated with ICPi, only seven cases of grade 3 or higher hyperthyroidism (0.10% of total patients; 3.6% of patients who developed hyperthyroidism) were reported (3). Rarely, ICPis can cause life-threatening thyroid storm due to severe thyrotoxicosis, which may manifest with hyperpyrexia and shock (223, 224).

Hypothyroidism

As is true of many cases of ICPi-related thyrotoxicosis, the symptoms of ICPi-related hypothyroidism are often mild and nonspecific. Fatigue and weight gain are the most common symptoms reported by patients who develop ICPi-related hypothyroidism (156, 201, 209). Additional clinical manifestations of hypothyroidism include cold intolerance, constipation, and dry skin. Physical examination may reveal bradycardia, dry coarse skin, facial puffiness, periorbital edema, tongue swelling, and delayed relaxation of deep tendon reflexes. Most cases of ICPi-related hypothyroidism are mild to moderate (*i.e.,* grade 1 and 2); in a meta-analysis of 38 RCTs comprising a total of 7551 patients treated with ICPis, only nine cases of grade 3 or higher hypothyroidism were reported (0.12% of total patients; 1.9% of patients who developed hypothyroidism) (3). However, severe untreated hypothyroidism resulting in myxedema coma, characterized by decreased mental status and often hypothermia, has been reported with ICPi therapy (225).

Management of ICPi-related primary thyroid dysfunction

Given the prevalence of ICPi-related thyroid dysfunction and the rapid time course during which ICPi-related thyroid dysfunction may develop, we recommend regular monitoring of TFTs. In particular, we recommend measuring a baseline TSH and free T4 prior to ICPi initiation, as well as before each infusion for at least five cycles. Moreover, given that many symptoms of thyroid dysfunction (such as fatigue and changes in bowel movements) are fairly nonspecific and have a large overlap with symptoms commonly experienced in patients with malignancy, we recommend that providers consider checking a TSH and free T4 in any patient who is receiving or has received ICPi therapy who reports such symptoms.

Of note, it is important to differentiate between primary and secondary (central) hypothyroidism, because central hypothyroidism should prompt concern

"ICPi-related DM shares many clinical features with fulminant T1DM, a subtype of T1DM first described in Japan."

for hypophysitis and trigger further assessment for deficiencies in other anterior pituitary axes, particularly central adrenal insufficiency. Untreated adrenal insufficiency can be life-threatening if not promptly managed. In addition, it is critical that patients with concurrent hypothyroidism and adrenal insufficiency receive corticosteroid replacement prior to thyroid hormone replacement as initiation of thyroid hormone replacement in the setting of untreated adrenal insufficiency may precipitate adrenal crisis, as discussed earlier in this review. Primary hypothyroidism is characterized by an elevated TSH and a low free T4, whereas central hypothyroidism is characterized by a low free T4 with an inappropriately low or normal.

Thyrotoxicosis

Overt thyrotoxicosis is characterized by a low TSH and an elevated free T4. Subclinical thyrotoxicosis is characterized by a low TSH and a free T4 within reference range. Of note, a low TSH and a free T4 within reference range may also be consistent with central hypothyroidism and should raise the possibility of pituitary dysfunction due to hypophysitis. In such cases, the clinical context should be considered. Measurement of a T3 level may be helpful; if elevated, this is more suggestive of thyrotoxicosis. If central hypothyroidism due to hypophysitis is suspected, measurement of cortisol should be considered to assess for adrenal insufficiency.

Overt thyrotoxicosis is typically mild and can be managed supportively in most cases (201, 204). Beta-blockers (for example, with propranolol 10 to 30 mg PO three times a day as needed or atenolol 25 to 50 mg PO once daily as needed for pulse >100 beats per minute) can be used for management of symptoms mediated by increased beta-adrenergic tone such as tachycardia, palpitations, tremulousness, anxiety, and heat intolerance and should be discontinued after thyrotoxicosis resolves. There has been no systematic study regarding the impact of corticosteroids on the outcome of ICPi-related thyroid dysfunction. We do not routinely use high-dose corticosteroids to treat ICPi-related thyrotoxicosis in our own practice, but in patients with severe thyrotoxicosis or elderly patients with cardiovascular comorbidities, high-dose systemic corticosteroids can be considered. We do not use antithyroid drugs in the treatment of ICPi-related thyrotoxicosis unless Graves disease is diagnosed, because the etiology underlying ICPi-related thyrotoxicosis is thyroiditis, not increased thyroid hormone synthesis. For patients with ICPi-related thyrotoxicosis, both overt and subclinical, we recommend serial monitoring of TSH and free T4 every 2 to 3 weeks because ICPi-related thyrotoxicosis may rapidly progress to hypothyroidism, as demonstrated by two patients treated with nivolumab who developed ICPi-related thyroid dysfunction whose TSH increased from normal to >50 within 4 weeks (210).

Hypothyroidism

Overt hypothyroidism is characterized by an elevated TSH and a low free T4. Subclinical hypothyroidism is characterized by an elevated TSH and a free T4 within reference range. If overt ICPi-related hypothyroidism develops, we recommend initiating thyroid hormone replacement with levothyroxine at a dose of 0.8 μg/kg daily in young patients without a history of cardiovascular disease. Our rationale behind this starting dose is discussed earlier. We also recommend considering levothyroxine initiation in patients with subclinical hypothyroidism whose TSH is ≥ 10 mIU/L (226). We recommend repeating TSH and free T4 measurements 4 to 6 weeks after levothyroxine initiation and titrating levothyroxine further based on these results. For patients with known coronary heart disease, we recommend initiating levothyroxine at a lower dose (*e.g.,* 12.5 to 25 μg PO daily), repeating TSH and free T4 measurements 4 to 6 weeks after levothyroxine initiation, and titrating the dose accordingly based on symptoms and TFTs (166). Also, for older patients (such as those over 65 years), it may be reasonable to start levothyroxine at a lower dose, monitor TFTs more frequently, and aim for a higher TSH goal of 4 to 6 mIU/L, given that (1) older patients are more susceptible to adverse effects of thyroid hormone overreplacement such as atrial fibrillation and osteoporotic fractures, (2) levothyroxine doses needed to normalize serum TSH are generally lower in older individuals compared with younger individuals, and (3) normal serum TSH ranges are higher in older populations (166).

Preexisting hypothyroidism

Patients with preexisting hypothyroidism who are being treated with ICPi therapy should continue to have their TFTs closely monitored, as thyroid hormone replacement requirements may change after initiation of ICPi therapy. One study found that in three patients with preexisting hypothyroidism on levothyroxine treatment, severe hypothyroidism developed after initiation of pembrolizumab that was not attributable to colitis or medications that increase hepatic metabolism of levothyroxine, requiring a doubling of levothyroxine dosing (207). Two other studies also describe patients with preexisting hypothyroidism who eventually required levothyroxine dose increases after ICPi initiation (75, 208). Transient thyrotoxicosis may also occur in these patients (201).

Thyroid autoantibodies and thyroid imaging

Given that the vast majority of cases of thyrotoxicosis resolve spontaneously or convert to hypothyroidism and are not associated with Graves disease, routine measurement of thyroid autoantibodies, including TPO Ab, TgAb, and TRAb (including TSI and thyrotropin binding inhibitory immunoglobulin), has not been demonstrated to be helpful. Similarly, thyroid imaging is of limited value. Thyroid ultrasound may

show variable findings or findings consistent with thyroiditis, such as a heterogeneous echotexture or diffuse hypoechogenicity (210, 211). Radioactive iodine or technetium-99m pertechnetate uptake typically shows decreased uptake consistent with thyroiditis (200, 201, 207, 211). Of note, many patients receiving ICPi therapy undergo frequent CT studies with iodine-based contrast enhancement, and exposure to iodine-based contrast decreases radioiodine uptake and limits the reliability of thyroid radioiodine uptake testing.

Measuring TSI and considering thyroid radioiodine uptake testing (provided the patient has not had recent iodine exposure for at least 1 month) may be helpful in unique cases of ICPi-related thyrotoxicosis in which a reasonable suspicion for Graves disease exists (such as the presence of a goiter, Graves orbitopathy, or persistent thyrotoxicosis).

18-fluorodeoxyglucose-positron emission tomography/CT (^{18}FDG-PET/CT) studies in patients with ICPi-related thyroid dysfunction may show diffuse increased uptake of ^{18}FDG consistent with an inflammatory thyroiditis (204, 207, 210). Given that this finding may be an early sign of thyroid dysfunction, we recommend that all patients with diffuse increased thyroid uptake of ^{18}FDG have a TSH and free T4 level checked.

ICPi continuation in the setting of thyroid dysfunction and use of corticosteroids in ICPi-induced thyroiditis

In the vast majority of cases of ICPi-related thyroid dysfunction, ICPi therapy was able to be continued without interruption. Accordingly, because ICPi-related thyroid dysfunction is a manageable condition with proper monitoring and treatment, ICPi therapy need not be discontinued in most mild to moderate cases of thyroid dysfunction. As discussed above, there has been no systematic study regarding the impact of high-dose corticosteroids on the outcome of ICPi-induced thyroid disorders. In our practice, we do not routinely use high-dose corticosteroids in patients who developed ICPi-related thyroid dysfunction.

ICPi-Related DM

Epidemiology of ICPi-related DM

ICPi type

ICPi-related DM is a rare but potentially life-threatening irAE due to ICPi therapy (Box 7). Nearly all cases of ICPi-related DM reported have been due to anti-PD-1 therapy. Several cases of DM related to anti-PD-L1 therapy have been reported as well; three cases have been reported in patients treated with atezolizumab (227–229), one case has been reported in a patient treated with durvalumab (229), and one case has been reported in a patient treated with combination avelumab and utomilumab, a mAb that binds to the protein receptor 4-1BB (CD137) (230). One additional case was reported in a patient on an unspecified anti-PD-L1 therapy (231). ICPi-related DM appears to be extremely rare with anti-CTLA-4 monotherapy; only two cases have been reported with development of ICPi-related DM on anti-CTLA-4 monotherapy (232, 233).

BOX 7. Key points of ICPi-related DM

- ICPi-related DM is a rare but potentially life-threatening ICPi-related irAE.
- Most cases of ICPi-related DM are due to anti-PD-1 or anti-PD-L1 therapy; ICPi-related DM due to anti-CTLA-4 therapy is rare.
- ICPi-related DM is characterized by (1) rapid onset of hyperglycemia, (2) swift progression of endogenous insulin deficiency, and (3) high risk of diabetic ketoacidosis (DKA) if not detected and treated promptly with insulin therapy.
- Patients who are receiving ICPi therapy and their families should receive counseling on symptoms and signs of hyperglycemia and DKA.
- DKA is a life-threatening complication of ICPi-related DM. Early detection of new-onset hyperglycemia and prompt initiation of insulin therapy and fluid resuscitation can prevent progression to DKA.
- ICPi-related DM appears to result in complete destruction of insulin secretory capacity and a need for long-term insulin. Multidose insulin treatment with basal-bolus insulin is the mainstay of treatment.

On review of the literature, we found 46 cases of ICPi-related DM for which clinical and diagnostic details were described. A summary of these reports is found in Table 5 and Table 6.

Demographics

Median age at presentation was 63 years old (range, 31 to 84 years old). For the 46 cases in which sex was available, 20 were women (43%). ICPi-related DM has been reported in white (230, 234, 242, 251, 255, 258), African-American (236, 241), Japanese (202, 243, 245–247), and Korean (252) patients. Of note, clinical studies and use of ICPi therapy are limited to several countries, which may contribute to differences in ethnicities that have been reported.

Natural history of ICPi-related DM

ICPi-related DM is characterized by several important features: (1) rapid onset of hyperglycemia, (2) swift progression of endogenous insulin deficiency, and (3) high risk of DKA if not detected and treated promptly with insulin therapy.

Doses of ICPi/time course

ICPi-related DM has been reported to occur as early as after a single dose of ICPi therapy (211, 237, 247) to as late as after 17 doses of ICPi therapy (239, 259). The time from initiation of anti-PD-1 or anti-PD-L1 therapy to presentation of ICPi-related DM ranged from 1 week (238) to 12 months (245, 259) (Table 6). The median number of doses of anti-PD-1/PD-L1 inhibitor therapy given prior to initial presentation of ICPi-related DM was four doses, on review of cases in

Table 5. Summary of Features of ICPi-Related DM in Case Reports

Feature	Findings
Median age at onset of ICPi-related DM	63 y old
Range of age at onset of ICPi-related DM	31–84 y old
Sex	20/46 (43%) female, 26/46 (57%) male
Race/ethnicity	Reported in white, African-American, Japanese, and Korean populations
Number of patients on each type of ICPi	
Anti-PD-1 therapy	39
Nivolumab (total)	23
Monotherapy	18
With concurrent ipilimumab	2
With prior ipilimumab	3
Pembrolizumab (total)	15
Monotherapy	8
With concurrent ipilimumab	2
With prior ipilimumab	5
Unspecified anti-PD-1 agent	1
Anti-PD-L1 therapy	6
Atezolizumab	3
Durvalumab	1
Avelumab (with concurrent utomilumab)	1
Unspecified anti-PD-L1 therapy	1
Anti-CTLA-4 therapy	1
Ipilimumab monotherapy	1
Median number of doses from first dose of anti-PD-1/PD-L1 therapy to ICPi-related DM presentation (range in parentheses)	3 doses (1–17 doses)
Range of time from first dose of PD-1/PD-L1 therapy to ICPi-related DM presentation	1 wk to 12 mo
Presentation of ICPi-related DM	
DKA (including initial hyperglycemia closely followed by DKA)	32/45 (71%)
Hyperglycemia without concurrent or subsequent reported DKA	13/45 (29%)
Median glucose at presentation (range in parentheses)	580 mg/dL (247–1015 mg/dL)
Median HbA1c at presentation (range in parentheses)	7.6% (5.8%–10.7%)
Autoimmune DM antibody positivity	
GAD (glutamic acid decarboxylase)	22/44 (50%)
IA2 (islet antigen 2)	3/20 (15%)
Insulin (IAA)	3/19 (16%)
Islet cell	2/20 (10%)
Zinc transporter 8 (ZnT8)	1/8 (13%)

which this information was available. In the single case report of DM related to ipilimumab monotherapy for which clinical information was available, DM developed after three doses of ipilimumab (233).

Patients with ICPi-related DM tend to have hemoglobin A1c (HbA1c) levels that are relatively low for the degree of hyperglycemia at presentation, reflecting the marked rapidity of progression of hyperglycemia. Median HbA1c at time of presentation of ICPi-related DM was 7.6% in the 37 cases in which a HbA1c at or close to the time of presentation was reported, compared with a median glucose on presentation of 580 mg/dL in the 38 cases in which a glucose on presentation was reported (Table 6).

Risk of DKA

In 32 of 45 cases (71%) of ICPi-related DM in which the clinical presentation was described, the development of DKA led to the diagnosis of ICPi-related DM (Table 6), reflecting the high risk of DKA and the rapid onset of endogenous insulin deficiency in cases of ICPi-related DM.

Similarities to fulminant T1DM

ICPi-related DM shares many clinical features with fulminant T1DM, a subtype of T1DM first described in Japan (262). Fulminant T1DM is characterized by the rapid onset of hyperglycemia with ketoacidosis, near-normal HbA1c levels despite marked hyperglycemia, and an absence of insulin secretion even at disease onset. In 2012, the Japan Diabetes Society published revised criteria for the diagnosis of fulminant T1DM (263). Specifically, fulminant T1DM is confirmed when all three of the following findings are present: (1) occurrence of diabetic ketosis or ketoacidosis soon (~7 days) after the onset of hyperglycemic symptoms (elevation of urinary and/or serum ketones at first visit), (2) plasma glucose $\geq$ 288 mg/dL and HbA1c $<$ 8.7% at first visit, and (3) urinary C-peptide excretion $<$ 10 μg/d or fasting serum C-peptide level $<$ 0.3 ng/mL and serum C-peptide $<$ 0.5 ng/mL after IV glucagon (or after a meal) at onset. Whether fulminant T1DM and ICPi-related DM share underlying pathophysiologic mechanisms remains to be determined.

Of note, several findings that are relatively common in many cases of fulminant T1DM do not appear to be common in ICPi-related DM. In particular, islet autoantibodies are generally undetectable in fulminant T1DM but were found in 50% of the case reports reviewed (Table 6). Moreover, elevation of serum pancreatic enzyme levels (lipase, amylase, or elastase-1) is observed in 98% of patients with fulminant T1DM but was not seen in many cases of ICPi-related DM, though pancreatic enzyme levels were not routinely reported in the available case reports of ICPi-related DM (263). Finally, flulike symptoms are commonly reported in fulminant T1DM but were uncommon in reported cases of ICPi-related DM.

Pathophysiology of ICPi-related DM

Autoimmune DM antibodies

Whether autoimmune DM antibodies are involved in the pathogenesis of ICPi-related DM or predict development of ICPi-related DM remains unclear. Autoimmune DM antibodies were positive in 22/44 (50%) of patients tested (Table 6). GAD autoantibodies were positive in all patients for whom at least one autoimmune DM antibody assayed was positive. Islet antigen 2 (IA2), insulin (IAA), islet cell, and zinc transporter 8 (ZnT8) autoantibodies have all been found to be positive in at least one case of ICPi-related DM (Table 6). However, elevated titers of these autoantibodies appear to be less prevalent than GAD, at least at the time of diagnosis of ICPi-related DM, with prevalences ranging between 10% and 15%, albeit for small numbers of patients (Table 6).

In three case reports, blood samples obtained prior to ICPi treatment initiation were tested for the presence of autoimmune DM antibodies. In two of the cases, autoantibodies were positive even prior to ICPi initiation. Gauci *et al.* (235) reported a patient who presented with DKA 6 weeks after starting nivolumab whose blood at presentation was positive for GAD, IA2, and ZnT8 autoantibodies. C-peptide was undetectable, indicating endogenous insulin deficiency (235). Analysis of frozen serum obtained at the start of and 3 months before starting nivolumab treatment showed positivity for these three autoantibodies; insulin, C-peptide, and glucose were normal at these times. Godwin *et al.* (236) described a patient who presented with DKA 4 weeks after starting nivolumab whose T1DM autoantibody profile after presentation was positive for GAD autoantibodies, IA2 autoantibodies, and IAA (after exogenous insulin administration). C-peptide was undetectable at presentation. Analysis of frozen serum obtained 8 months prior to the initiation of nivolumab was positive for GAD, IA2, and ZnT8 autoantibodies and negative for IA2 autoantibodies. ZnT8 autoantibodies were retested 13 months after development of DKA and had become negative.

In contrast, Lowe *et al.* (249) reported a patient who presented with DKA after three doses (40 days) of combination ipilimumab-nivolumab treatment. Biochemical testing during his hospitalization for DKA revealed positive GAD autoantibodies and C-peptide $<$ 0.1 ng/mL. Analysis of frozen serum obtained 1 month prior to ICPi treatment initiation showed negative GAD autoantibodies. In summary, these studies indicate that in some patients who develop ICPi-related DM, islet autoantibodies may be present prior to ICPi-related DM, whereas in other patients who develop ICPi-related DM, seroconversion may

Table 6. Summary of Cases of ICPi-Related DM

Study[a]	Age (y)/Sex	Malignancy	ICPi Agent	Number of Doses of Anti-PD-1/PD-L1 ICPi Prior to Presentation of ICPi-Related DM[b]	Time From First Anti-PD-1 or Anti-PD-L1 Dose to Presentation of ICPi-Related DM	Symptoms	DM Presentation/ glucose on Presentation (mg/dL)/ HbA1c (%)	GAD Antibody	IA2 Antibody	Insulin Antibody (IAA)	Islet Cell Antibody	ZnT8 Antibody	HLA	Other Autoimmune Conditions or ICPi-Related irAEs
Araujo *et al.* (234)	73/F	NSCLC	Nivolumab	2	n/a	Vomiting, confusion, polyuria, polydipsia for 12 h	DKA/>1000/7.2	+			—		DR3-DQ2; DR4-DQ8	
Gauci *et al.* (235)	73/M	Melanoma	Nivolumab	3	6 wk	Abdominal pain, vomiting, severe asthenia, polyuria, polydipsia	DKA/500/8.8	+	+			+	n/a	Graves disease
Godwin *et al.* (236)	34/F	NSCLC	Nivolumab	2	4 wk	Abdominal pain, nausea, weakness	DKA/739/7.1	+	+	+			A30:01, 30:02; D09:CTZ,09: CTZ	
Hofmann *et al.* (237) (1/4)	70/F	Melanoma	Nivolumab	4	6 wk	Increased thirst and circulatory problem	HG / n/a / n/a	—	—				n/a	Thyrotoxicosis
Hughes *et al.* (238) (2/5)	83/F	NSCLC	Nivolumab	n/a	<1 mo	n/a	DKA/350 /7.7	+		—	—		A2.1+, DR4+	
Hughes *et al.* (238) (3/5)	63/M	RCC	Nivolumab	n/a	4 mo	n/a	HG/247/8.2	+		+	+		A2.1+, DR4+	
Hughes *et al.* (238) (4/5)	58/M	SCLC	Nivolumab	n/a	1 wk	n/a	DKA/749/9.7	+		—	—		A2.1+	
Ishikawa *et al.* (239)	54/F	Melanoma	Nivolumab	17	n/a	Excessive thirst	HG/580/7.0	—	—				B*1:01, 40:06; DRB1*04:05, 04:06; DRB1*03:02, 04:01	
Kumagai *et al.* (240)	73/M	Lung adenocarcinoma	Nivolumab	11	n/a	Extreme fatigue, weight loss, thirst	HG/708/9.4	—	—			—	DRB*09:03-DQB1*03:03; DRB1*01:01-DQB*05:01	Pneumonitis,[c] vitiligo[c]
Li *et al.* (241)	63/M	Lung SCC	Nivolumab	n/a	27 d	Palpitations, fatigue	DKA/592/ n/a	+					n/a	Hypothyroidism[c]

(*Continued*)

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Table 6. *Continued*

Study[a]	Age (y)/Sex	Malignancy	ICPi Agent	Number of Doses of Anti-PD-1/PD-L1 ICPi Prior to Presentation of ICPi-Related DM[b]	Time From First Anti-PD-1 or Anti-PD-L1 Dose to Presentation of ICPi-Related DM	Symptoms	DM Presentation/ glucose on Presentation (mg/dL)/ HbA1c (%)	GAD Antibody	IA2 Antibody	Insulin Antibody (IAA)	Islet Cell Antibody	ZnT8 Antibody	HLA	Other Autoimmune Conditions or ICPi-Related irAEs
Marchand *et al.* (242)	55/M	Pulmonary pleomorphic carcinoma	Nivolumab	9	n/a	Sudden worsening of performance status, acute polyuria and polydipsia	DKA/499/8.2	—	—	—	—	—	n/a	Hypophysitis with secondary adrenal insufficiency[c]
Matsumura *et al.* (243)	68/M	Lung adenosquamous carcinoma	Nivolumab	3	40 d	n/a	HG/330/8.0	—	—	—			A*24:02, DRB1*09:01, DRB1*15:02	
Miyoshi *et al.* (244)	66/F	Melanoma	Nivolumab	6	121 d	Anorexia, nausea, vomiting	DKA/531/7.3	—	—			—	DRB1*11:01, 13:02:01, DQB1*03:01:01, 06:04:01	
Munakata *et al.* (202)	72/M	Hodgkin lymphoma	Nivolumab	6	n/a	None	HG/375/7.3	—			—	—	B*4002	
Okamoto *et al.* (245)	55/F	Melanoma	Nivolumab	n/a	12 mo	n/a	HG, ketonuria/ 580/7.0	—	—			—	DRB1*04:05-DQB1*04:01	
Teramoto *et al.* (246)	63/F	Melanoma	Nivolumab	8	n/a	Fatigue, polyuria, polydipsia	DKA/661/8.9	—	—	—			n/a	
Usui *et al.* (247) (1/2)	31/F	NSCLC	Nivolumab	1	13 d	Fatigue, nausea	DKA/743/6.4	+					DRB1*04:05-DQB1*04:01	
Usui *et al.* (247) (2/2)	62/F	NSCLC	Nivolumab	4	n/a	Excessive thirst, polyuria	HG/246/6.5	—					DRB1*09:01-DQB1*03:03	
Alzenaidi *et al.* (248)	47/M	Melanoma	Nivolumab[d]	2	n/a	Lethargy, confusion, vomiting, abdominal pain	DKA / n/a / 8.0	+			—		n/a	
Lowe *et al.* (249)	54/M	Melanoma	Nivolumab[d]	3	40 d	Extreme weakness, myalgias, nausea, vomiting	DKA / n/a / n/a	+					A2, DQB1*0602	AITD, skin rash, autoimmune hepatitis, autoimmune colitis, hypophysitis
Hofmann *et al.* (237) (2/4)	78/F	Melanoma	Nivolumab[e]	n/a	3 wk	Vomiting, diarrhea	DKA / n/a / n/a	+	—				n/a	

(*Continued*)

Table 6. *Continued*

Study[a]	Age (y)/Sex	Malignancy	ICPi Agent	Number of Doses of Anti-PD-1/PD-L1 ICPi Prior to Presentation of ICPi-Related DM[b]	Time From First Anti-PD-1 or Anti-PD-L1 Dose to Presentation of ICPi-Related DM	Symptoms	DM Presentation/ glucose on Presentation (mg/dL)/ HbA1c (%)	GAD Antibody	IA2 Antibody	Insulin Antibody (IAA)	Islet Cell Antibody	ZnT8 Antibody	HLA	Other Autoimmune Conditions or ICPi-Related irAEs
Hofmann *et al.* (237) (4/4)	40/M	Melanoma	Nivolumab[e]	n/a	6 wk	n/a	n/a / n/a / n/a						n/a	
Hughes *et al.* (238) (1/5)	55/F	Melanoma	Nivolumab[e]	n/a	5 mo	n/a	DKA/532/6.9	—		—	—		A2.1+, DR4+	AITD
Chae *et al.* (250)	76/M	Lung adenocarcinoma	Pembrolizumab	2	~29 d	None	HG/616/5.8	+	+	—	—		n/a	
Gaudy *et al.* (251)	44/F	Melanoma	Pembrolizumab	n/a	2 wk	Vomiting, confusion, polyuria, polydipsia, weight loss	DKA/908/6.85						n/a	AITD
Hughes *et al.* (238) (5/5)	64/F	Melanoma	Pembrolizumab	n/a	<1 mo	n/a	HG, ketonuria/ 703/7.4	—		—	—		DR4+	AITD
Kong *et al.* (252)	68/M	Lung SCC	Pembrolizumab	7	n/a	Vomiting (with DKA presentation)	HG, followed by DKA/866/7.9	—		—			DRB1*0901-DQB1*0303; DRB1*1405-DQB1*0503	Subclinical thyrotoxicosis[c]
Leonardi *et al.* (253)	66/M	Lung adenocarcinoma	Pembrolizumab	3	n/a	Fatigue, polyuria, polydipsia	DKA/636/7.6	+		—	—		n/a	
Mizab Mellah *et al.* (254)	58/M	Melanoma	Pembrolizumab	n/a	3 mo	Polydipsia, polyuria, anorexia, asthenia for 4 d	DKA/602/7.4	—	—				n/a	
Smith-Cohn *et al.* (255)	67/F	Cholangio-carcinoma	Pembrolizumab	9	n/a	Severe nausea, vomiting, fatigue, abdominal pain	DKA/475/8.7	+	—		—	—	n/a	
Thoreau *et al.* (256)	73/M	Melanoma	Pembrolizumab	n/a	26 wk	Painful, cyanotic, cold left foot	DKA / n/a / n/a	—	—				n/a	
Scott *et al.* (196)	58/M	Melanoma	Pembrolizumab[d]	n/a	62 d	n/a	DKA/661/6.8	—	—	—	—		n/a	Subclinical thyrotoxicosis

(*Continued*)

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Table 6. *Continued*

Study[a]	Age (y)/Sex	Malignancy	ICPi Agent	Number of Doses of Anti-PD-1/PD-L1 ICPi Prior to Presentation of ICPi-Related DM[b]	Time From First Anti-PD-1 or Anti-PD-L1 Dose to Presentation of ICPi-Related DM	Symptoms	DM Presentation/ glucose on Presentation (mg/dL)/ HbA1c (%)	GAD Antibody	IA2 Antibody	Insulin Antibody (IAA)	Islet Cell Antibody	ZnT8 Antibody	HLA	Other Autoimmune Conditions or ICPi-Related irAEs
Alhusseini and Samantray (257)	65/M	Lung adenocarcinoma	Pembrolizumab[d]	1	3 wk	Vomiting	DKA/525/8.5	+		—	—		n/a	Hypothyroidism[c]
Aleksova *et al.* (258)	60/M	Melanoma	Pembrolizumab[e]	n/a	5 wk	Polyuria, polydipsia	DKA/486/7.1	—	—				n/a	
Hofmann *et al.* (237) (3/4)	58/F	Melanoma	Pembrolizumab[e]	1	3 wk	Increased thirst, persistent urge to urinate	HG / n/a / n/a	+	—				n/a	
Hansen *et al.* (259)	58/M	Melanoma	Pembrolizumab[e]	17	~12 mo	Fungal-appearing inguinal rash, worsening fatigue, weight loss, polydipsia, polyuria	HG/408/9.7	+			—		n/a	Hypothyroidism, hair depigmentation
Humayun and Poole (260)	55/M	Melanoma	Pembrolizumab[e]	9	n/a	Tiredness, polyuria, polydipsia	DKA/756/10.7	—			—		n/a	Hypophysitis with panhypopituitarism, autoimmune arthropathy, skin rash[c]
Martin-Liberal *et al.* (261)	54/F	Melanoma	Pembrolizumab[e]	3	n/a	Lethargy, vomiting, polydipsia, polyuria	DKA / n/a / n/a	+		—	—		DRB1*04, DQB1*0302 (A2 DR4 DQ8)	Asthma
Mellati *et al.* (231) (2/2)	66/F	SCC of the jaw	PD-1 antibody	n/a	7 wk	n/a	DKA/752/9.4	+	—	—		—	DR3-DQ2/ DR4-DQ8	
Patti *et al.* (227)	70/F	Lung adenocarcinoma	Atezolizumab	3	n/a	n/a	DKA / 1015 / n/a	—					n/a	Asthma
Hickmott *et al.* (228)	57/M	Urothelial cancer	Atezolizumab	5	15 wk	Polydipsia, weight loss, fatigue	DKA/432/7.5	—			—		DRB1*11, DRB1*04; DRB3*02; DRB4*01; DQB1*03, DQB1*03	

(*Continued*)

Table 6. *Continued*

Study[a]	Age (y)/Sex	Malignancy	ICPi Agent	Number of Doses of Anti-PD-1/PD-L1 ICPi Prior to Presentation of ICPi-Related DM[b]	Time From First Anti-PD-1 or Anti-PD-L1 Dose to Presentation of ICPi-Related DM	Symptoms	DM Presentation/ glucose on Presentation (mg/dL)/ HbA1c (%)	GAD Antibody	IA2 Antibody	Insulin Antibody (IAA)	Islet Cell Antibody	ZnT8 Antibody	HLA	Other Autoimmune Conditions or ICPi-Related irAEs
Way *et al.* (229) (2/2)	n/a / M	Papillary urothelial carcinoma	Atezolizumab	3	9 wk	Fatigue, polyuria	HG/379/8.2	+			—		(DQ8 negative)	
Atkins and Thompson (230)	50/M	SCC of the tonsil	Avelumab[f]	2	1 mo	n/a	DKA/340/6.4	+		—			n/a	
Way *et al.* (229) (1/2)	84/F	SCC of the nasopharynx	Durvalumab	11	18 wk	Polyuria, polydipsia, fatigue	HG, followed by DKA/488/9.1	+					n/a	
Mellati *et al.* (231) (1/2)	70/M	Lung adenocarcinoma	PD-L1 antibody	5	15 wk	n/a	DKA/411/9.8	—		—			n/a	
Tsiogka *et al.* (233)	64/M	Melanoma	Ipilimumab	3	n/a	Vomiting, polydipsia, transient fever, progressive confusion	DKA/750/6.1	—	—	—	—		DRB1*0708 DQB1*0204	Skin rash, hypophysitis[c]

Abbreviations: F, female; GAD, glutamic acid decarboxylase; HG, hyperglycemia; IA2, islet antigen 2; M, male; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; ZnT8, zinc transporter 8.

[a]Studies that described multiple cases are listed individuals, with the case number in order of description within the study followed by the total number of cases.

[b]For Tsiogka *et al.* (233) (the only case of ICPi-related DM due to anti-CTLA-4 monotherapy for which clinical details have been described), the number of doses listed is the number of doses of ipilimumab given before diagnosis of ICPi-related DM.

[c]irAE developed concurrently or after ICPi-related DM developed.

[d]Received ipilimumab concurrently.

[e]Received ipilimumab prior to anti-PD-1/PD-L1 therapy.

[f]Received utomilumab (anti-4-1BB mAb) concurrently.

occur after the initiation of ICPi therapy. These reports also indicate that baseline autoimmune DM antibody testing may not be particularly useful as biomarkers to predict individuals susceptible to ICPi-related DM.

HLA typing and CTLA-4, PD-1, and PD-L1 polymorphisms

A strong genetic component underlies susceptibility to developing T1DM (264). In particular, polymorphisms in the genes that encode HLA class II genes on chromosome 6p21 in the major histocompatibility complex (MHC) confer the strongest genetic risk for T1DM. The MHC region is estimated to account for 41% of the familial clustering of T1DM (265). In a number of cases of ICPi-related DM, HLA typing in affected patients has revealed HLA types that confer genetic susceptibility (202, 228, 243, 245, 247, 252, 261). Interestingly, an association with HLA DRB1*04:05-DQB1*04:01 is reported with fulminant T1DM, and this HLA type was found in two patients with ICPi-related DM (245, 247).

Although specific *CTLA-4*, *PD-1*, and *PD-L1* polymorphisms have been associated with increased susceptibility to development of T1DM, to the best of our knowledge, these polymorphisms have not been studied in patients who have developed ICPi-related DM.

Clinical, biochemical, and imaging manifestations of ICPi-related DM

Clinical manifestations

Patients with ICPi-related DM may present with symptoms and signs of hyperglycemia (*e.g.,* polyuria, polydipsia, and weight loss) or ketoacidosis (*e.g.,* nausea, vomiting, abdominal pain, hyperventilation/tachypnea, lethargy, obtundation, seizure, or coma). Hyperglycemia may be detected incidentally, especially given the frequency with which laboratory tests such as plasma glucose are obtained as part of routine monitoring for patients being treated with ICPi therapy. Occasionally, patients are asymptomatic, and incidental discovery of new hyperglycemia is the primary indicator of ICPi-related DM; in these cases, prompt recognition of marked hyperglycemia and treatment with insulin can prevent progression to DKA (202, 250).

HbA1c

HbA1c (also called glycated Hb) provides a measure of mean blood glucose over the prior 8 to 12 weeks. Hb in new red blood cells is minimally glycated; as these red blood cells circulate, glucose enters them freely and becomes irreversibly attached to Hb. Thus, the level of glycated Hb reflects the mean blood glucose concentration over the lifespan of the red blood cell. HbA1c is commonly used as a screening test for T2DM (266). HbA1c is elevated in most cases of ICPi-related DM (Table 6). However, its sensitivity for detecting ICPi-related DM may be somewhat limited, as emphasized above, given the rapid time course of development of ICPi-related DM. Marked hyperglycemia in the setting of a normal or only mildly elevated HbA1c should still raise suspicion for the development of ICPi-related DM.

C-peptide

C-peptide is a widely used measure of endogenous insulin secretion. Pancreatic β cells synthesize the prohormone proinsulin, which is cleaved to produce insulin and C-peptide in equimolar amounts. C-peptide can be measured in the blood or urine to assess endogenous insulin secretion and can be measured in different contexts, including random, fasting, postprandial, after a mixed meal tolerance test, and after glucagon stimulation (267). C-peptide measured in various contexts in cases of ICPi-related DM has been low in nearly all cases, consistent with substantial impairment in endogenous insulin secretion. Specific cutoffs for C-peptide levels have not been determined for ICPi-related DM. Of note, because C-peptide is removed by the kidneys, C-peptide levels need to be interpreted with caution in the setting of renal dysfunction.

Pancreatic imaging

Pancreatic imaging has been described in a number of patients with ICPi-related DM and has shown marked abnormalities in some cases and unremarkable findings in other cases (202, 233, 234, 239, 244, 245, 252, 255, 256). CT, MR, or ultrasound of the pancreas may show progressive pancreatic atrophy, pancreatic enlargement, and findings consistent with diffuse pancreatic inflammation. However, pancreatic imaging may also be normal or unremarkable. Pancreatic inflammation has also been detected at the onset of non-ICPi-related fulminant T1DM (268).

Preexisting, concurrent, or subsequent autoimmune disease/irAEs and DM

Most patients who developed ICPi-related DM had no preexisting autoimmune disease prior to ICPi initiation. Two had preexisting asthma (227, 261) and four had preexisting AITD (including Graves disease) (235, 238, 251) prior to ICPi initiation. Only one case described a family history of autoimmune DM, in which the patient had two grandchildren with T1DM (255); in all other cases reviewed, there was no family history of autoimmune DM or family history was not described.

No personal history of prediabetes or diabetes was noted in the large majority of cases. Preexisting prediabetes was present in two cases (250, 253), preexisting T2DM not treated with insulin was present in four cases (237, 238, 248, 257), and preexisting noninsulin-dependent pancreatic diabetes was present in one case due to prior pancreaticoduodenectomy (243).

Several patients who developed ICPi-related DM developed irAEs prior to, concurrent with, or subsequent

to the development of ICPi-related DM. These included endocrine irAEs such as hypophysitis (233, 242, 249, 260) and thyroid dysfunction (196, 237, 241, 249, 256, 257, 259), as well as nonendocrine irAEs such as pneumonitis (240), skin rash (233, 249, 260), vitiligo or hair depigmentation (240, 249, 259, 260), hepatitis (249), colitis (249), and arthropathy (260).

Management of ICPi-related DM

Counseling on symptoms and signs of hyperglycemia and ketoacidosis

Given the rarity but high morbidity and rapid onset of ICPi-related DM, patients and their families should be counseled on the symptoms and signs of hyperglycemia and ketoacidosis prior to the onset of ICPi initiation, particularly in patients who will be starting anti-PD-1 therapy. If patients report symptoms or signs of hyperglycemia (as described earlier), glucose levels should be checked, and evaluation for ketoacidosis with serum or urine ketones and an arterial or venous blood gas should be considered.

Management of hyperglycemia

If new or worsening hyperglycemia is discovered on routine laboratory monitoring, such as routine plasma glucose levels drawn in the context of oncologic or other medical care, the presence of DKA should be assessed (*e.g.*, with a basic metabolic panel to assess electrolytes, bicarbonate, and anion gap, and measurement of serum or urine ketones and an arterial or venous blood gas if suspicion for DKA is high) and close monitoring of glucose levels should be initiated. C-peptide measurement in blood or urine may be helpful to assess endogenous insulin production; low C-peptide levels should prompt a high suspicion for ICPi-related DM, and initiation of insulin therapy should be strongly considered. Inpatient admission for close glycemic monitoring may be reasonable and has led to prompt diagnosis of ICPi-related DM and avoidance of development of DKA in several cases (202, 237). Urgent referral to and clinical coordination with an endocrinologist is recommended.

Management of DKA

DKA should be managed with vigorous intravenous fluid replacement, correction of electrolyte abnormalities, and insulin therapy. Detailed recommendations for management of DKA are available elsewhere (269).

Long-term insulin needs

ICPi-related DM nearly invariably results in a long-term need for insulin. In only one reported case of ICPi-related DM was a patient able to discontinue insulin, 54 days after initial presentation (259). Of note, this patient presented with hyperglycemia but did not have reported DKA, and C-peptide remained detectable on serial measurements performed over several weeks following his diagnosis of ICPi-related DM.

ICPi continuation

Given that DM is treatable and the need for insulin therapy appears to be permanent in nearly all cases of ICPi-related DM, ICPi therapy has been continued in most cases of ICPi-related DM.

Systemic corticosteroid therapy

Similar to other endocrine irAEs and unlike many nonendocrine irAEs, there does not appear to be a role for corticosteroids in the treatment of ICPi-related DM, although evidence for this remains extremely limited. Four cases of ICPi-related DM report trials of systemic corticosteroids; none was successful in reversing the ICPi-related DM. These cases are summarized in Table 7.

Table 7. Summary of Cases of ICPi-Related DM Treated With Systemic Corticosteroids

Study	Patient Description and Malignancy	Clinical Presentation	Steroids	Outcome
Aleksova *et al.* (258)	60-y-old man with melanoma	DKA after second dose of pembrolizumab	Prednisone at 2 mg/kg for 3 d, then 1 mg/kg for 10 d, followed by a weaning schedule for a total of 6 wk of treatment	Continued to require insulin
Chae *et al.* (250)	76-y-old man with lung adenocarcinoma	Asymptomatic hyperglycemia after second dose of pembrolizumab	Prednisone 10 mg PO daily ×25 d (of note, this was started 21 d after presentation of hyperglycemia)	Continued to require insulin
Smith-Cohn *et al.* (255)	67-y-old woman with cholangiocarcinoma	DKA after ninth dose of pembrolizumab	Methylprednisolone 125 mg IV once followed by prednisone 60 mg PO daily, tapered over 2 wk	Continued to require insulin
Lowe *et al.* (249)	54-y-old man with melanoma	DKA and secondary adrenal insufficiency after third dose of combination ipilimumab-nivolumab	Methylprednisolone followed by prednisone (doses not recorded; unclear if these were replacement doses or immunosuppressive doses)	Continued to require insulin

ICPi-Related PAI

Introduction

ICPi therapy is a rare cause of PAI and has been reported in a few cases (Box 8). It is important to keep in mind that the differential diagnosis for adrenal insufficiency in the setting of ICPi therapy and malignancy includes several possibilities. Central adrenal insufficiency can be caused by ICPi-related hypophysitis or pituitary metastasis. PAI may be due to ICPi-related PAI, bilateral adrenal metastases, or bilateral adrenal hemorrhage, leading to adrenocortical destruction and/or impairment. Other causes of adrenal insufficiency include infection, drugs, infiltrative disease, and syndromic conditions and are summarized elsewhere (169, 198, 270). Central and PAI need to be distinguished from one another, as PAI requires mineralocorticoid replacement in addition to glucocorticoid replacement. This is because in central adrenal insufficiency, the adrenal zona glomerulosa, which synthesizes aldosterone, remains intact, and mineralocorticoid production is preserved. In contrast, in PAI, the zona glomerulosa is impaired, and mineralocorticoid deficiency typically results. In central adrenal insufficiency, the zona fasciculata, which synthesizes cortisol, undergoes atrophy over the course of several weeks due to prolonged lack of stimulation from ACTH. The zona glomerulosa remains intact in central adrenal insufficiency because it is primarily regulated by the renin-angiotensin system.

Incidence and epidemiology of ICPi-related PAI

PAI is a rare complication of ICPi therapy. Only a few case reports describing ICPi-related PAI have been published (271–274). The incidence of ICPi-related PAI is difficult to estimate in part because many clinical trials involving ICPi therapy report adrenal insufficiency as an adverse event but do not specify whether the adrenal insufficiency is primary or central in etiology.

Pathophysiology of ICPi-related PAI

The pathogenesis of ICPi-related PAI is not well understood. Elevated levels of 21-hydroxylase and adrenal cortex antibody titers were found in one patient who developed pembrolizumab-related PAI (271). Whether adrenal autoantibodies play a role in pathogenesis, prediction, or prognosis of ICPi-related PAI remains unclear.

Clinical, biochemical, and imaging manifestations of ICPi-related PAI

A summary of cases of ICPi-related PAI and adrenalitis reported in the literature for which clinical information is available is shown in Table 8.

Clinical manifestations

Symptoms and signs of adrenal insufficiency are nonspecific and include fatigue, postural dizziness, orthostatic hypotension, anorexia, weight loss, and abdominal discomfort (198). Adrenal crisis is life-threatening and is characterized by severe weakness, syncope, nausea, vomiting, abdominal pain, confusion, altered mental status, and delirium that can progress to shock and death if untreated (198).

Biochemical manifestations

Hyponatremia and hyperkalemia are common in PAI due to the presence of both glucocorticoid and mineralocorticoid deficiency; less commonly, hypoglycemia and hypercalcemia can be seen (198).

Imaging manifestations

Abdominal imaging in ICPi-related PAI may show evidence of adrenalitis, reflected in bilateral enlarged adrenal glands with relatively smooth borders (Fig. 6). Adrenal metastases should be considered in the differential diagnosis of unilateral or bilateral adrenal gland enlargement in the setting of malignancy and typically result in a nodular appearance and/or distortion of adrenal anatomy on imaging. Transient increased ^{18}FDG uptake in the adrenal glands consistent with adrenalitis has been reported.

In the three cases of ICPi-related PAI in the literature in which abdominal imaging was available at the time of diagnosis, one showed normal-appearing bilateral adrenal glands on abdominal CT (271), one showed uniformly increased ^{18}FDG activity in the bilateral adrenal glands (272), and one showed bilateral enlargement of the adrenal glands on abdominal CT (273). Follow-up imaging may show normalization (273) or atrophy (271) of the adrenal glands.

Bacanovic *et al.* (275) described a case of ipilimumab-induced adrenalitis confirmed on imaging without concurrent frank adrenal insufficiency. Adrenalitis was diagnosed based on an ^{18}FDG-PET/CT scan that

BOX 8. Key points regarding ICPi-related PAI

- PAI is a rare irAE associated with ICPi therapy. Only a few cases have been described in the literature.
- PAI has been reported with ipilimumab, nivolumab, and pembrolizumab therapy.
- PAI is characterized biochemically by a low or relatively low cortisol level in the setting of an elevated ACTH level. Cosyntropin stimulation in PAI shows an inadequate rise in cortisol in response to cosyntropin. Aldosterone levels tend to be low (mineralocorticoid deficiency) and renin levels tend to be elevated in PAI due to failure of the zona glomerulosa of the adrenal gland.
- PAI must be distinguished from central adrenal insufficiency. In contrast to central adrenal insufficiency, PAI requires mineralocorticoid replacement in addition to glucocorticoid replacement.

Table 8. Summary of Cases of ICPi-Related PAI and Adrenalitis

Study	Age/Sex/ Malignancy	ICPi/Number of ICPi Doses Prior to Adrenal Presentation/ Time From First ICPi Dose to Adrenal Presentation	Clinical Presentation	Laboratory Testing	PAI Diagnosed?	Adrenal Imaging	Other Autoimmune Conditions
Paepegaey *et al.* (271)	55 F Melanoma	Pembrolizumab 10 doses 10 mo	General physical health deterioration, hypotension, hypothermia, hypoglycemia, hyponatremia, hyperkalemia, acute kidney injury	- Cortisol < 0.51 μg/dL - Cortisol after cosyntropin stimulation test (cosyntropin dose and timeframe after cosyntropin administration not reported) < 0.51 μg/dL - ACTH 400 pg/mL (reference range < 59) - Sodium 115 mmol/L - Potassium 5.7 mmol/L −21-hydroxylase antibody 1.9 U/L (reference range < 1) - Adrenal cortex antibody 20 (reference range 0) - Aldosterone undetectable - Renin (after high dose glucocorticoid) 23 mcIU/mL (reference range, 9–72)	Yes	CT abdomen: No increase in adrenal gland size was found. Repeat CT abdomen 2 mo later showed atrophied adrenal glands.	ICPi-related hypothyroidism (preceding diagnosis of ICPi-related PAI)
Trainer *et al.* (272)	43 M Melanoma	Nivolumab 4 doses 8 wk	Fatigue, anorexia, weight loss, postural symptoms	- Random serum cortisol 7.0 μg/dL - Cosyntropin (250 μg) stimulation test: 6.7 (baseline) → 5.7 (30 min postcosyntropin) → 6.2 (60 min postcosyntropin) - ACTH 200 pg/mL - Sodium 127 mmol/L - Renin 19.8 nmol/L/h - Aldosterone < 3.6 ng/dL	Yes	^{18}FDG-PET/CT: Uniformly increased FDG activity in bilateral adrenal glands; subsequent ^{18}FDG/PET-CT scan showed normal appearance of the adrenal glands.	None reported
Min and Ibrahim (273)	56 F Melanoma	Ipilimumab 4 doses n/a	Fatigue, headache	- Cortisol (morning) low (exact level not reported) - ACTH (morning) low (exact level not reported) - Cosyntropin stimulation test (cosyntropin dose and timeframe after cosyntropinadministration not reported) showed failure of cortisol and aldosterone to respond	Yes	CT abdomen: Bilateral enlargement of adrenal glands. Repeat CT abdomen 6 wk later showed normalization of size of bilateral adrenal glands.	ICPi-related hypophysitis with secondary adrenal insufficiency (concurrent with diagnosis of ICPi-related PAI)

(*Continued*)

Table 8. *Continued*

Study	Age/Sex/ Malignancy	ICPi/Number of ICPi Doses Prior to Adrenal Presentation/ Time From First ICPi Dose to Adrenal Presentation	Clinical Presentation	Laboratory Testing	PAI Diagnosed?	Adrenal Imaging	Other Autoimmune Conditions
Yang *et al.* (274)	n/a M RCC	Ipilimumab n/a n/a	n/a	- Cortisol low (exact level not reported) - ACTH elevated (exact level not reported)	Yes	n/a	ICPi-related hypophysitis (concurrent with diagnosis of ICPi-related PAI)
Bacanovic *et al.* (275)	79 F Melanoma	Ipilimumab 4 doses 2 mo	n/a	- Cortisol 21 μg/dL (reference range, 2.3–11.9)	No	^{18}FDG-PET/CT: Smooth thickening of bilateral adrenal glands with increased ^{18}FDG uptake in both adrenal glands. Baseline (prior to ipilimumab initiation) and follow-up ^{18}FDG-PET/CT scans (4 mo later) showed normalization in size and metabolic activity of both adrenal glands.	None reported

Cases are arranged by ICPi therapy.
Abbreviation: RCC, renal cell carcinoma.

showed bilateral adrenal gland thickening with increased ^{18}FDG uptake in both adrenal glands, both new findings compared with baseline ^{18}FDG-PET/CT scan prior to ipilimumab initiation. However, PAI did not develop in this patient, and follow-up ^{18}FDG-PET/CT scan 4 months later showed normalization in the size and metabolic activity of both adrenal glands, suggesting that ICPi-related adrenalitis may not always result in frank adrenal insufficiency.

Management

Monitoring

In a patient with symptoms or signs concerning for adrenal insufficiency, obtaining a baseline ACTH and cortisol measurement prior to administration of corticosteroids can be helpful for diagnostic purposes, if safe to do so. However, in acutely ill patients with clinical symptoms and signs of adrenal insufficiency, empiric treatment with corticosteroids should not be delayed. An elevated ACTH (*e.g.,* greater than twofold the upper limit of the reference range) in the setting of a low or low-normal morning cortisol is consistent with PAI (198). Cosyntropin stimulation testing can also be helpful in the diagnostic workup of adrenal insufficiency (198), as outlined earlier in this review. Of note, an inadequate rise in cortisol is not specific to PAI and can be seen in cases of central adrenal insufficiency of several weeks' or more duration due to atrophy of the adrenal glands from decreased endogenous ACTH.

Measurement of plasma renin (*e.g.,* plasma renin activity or concentration) and aldosterone can be helpful to determine if mineralocorticoid deficiency consistent with PAI is present. Aldosterone is low and plasma renin levels are elevated in PAI. These tests may need to be interpreted appropriately in the setting of IV fluids, which can influence the levels of renin and aldosterone. Measurement of an aldosterone level as part of a cosyntropin stimulation test can also be helpful to diagnose mineralocorticoid deficiency and PAI. An aldosterone level measured 30 minutes after administration of 250 μg of IV cosyntropin that is below 5 ng/dL is indicative of mineralocorticoid deficiency (276).

Measuring aldosterone after cosyntropin stimulation can be particularly helpful in diagnosing PAI when it may coexist with hypophysitis and central adrenal insufficiency, as illustrated by a case reported by Min and Ibrahim (273). When central adrenal insufficiency and PAI coexist, biochemical testing may show a low ACTH and low cortisol. In central adrenal insufficiency, the zona glomerulosa remains intact because it is primarily under the regulation of the renin and angiotensin, not ACTH. ACTH, however,

can stimulate aldosterone secretion from the zona glomerulosa independent from renin and angiotensin stimulation. Thus, in the setting of an intact zona glomerulosa, aldosterone levels rise in response to cosyntropin stimulation. In contrast, in PAI, the zona glomerulosa is affected and aldosterone levels fail to rise in response to cosyntropin stimulation.

The utility of measuring adrenal autoantibodies has not been studied in ICPi-related PAI.

Glucocorticoid and mineralocorticoid replacement

Stress dose corticosteroids should be immediately administered to any patient with known adrenal insufficiency who presents with an acute adrenal crisis or critical illness. They should also be considered as part of empiric treatment in critically ill patients who present with symptoms or signs concerning for adrenal insufficiency. A typical stress dose of corticosteroids includes an initial dose of hydrocortisone 100 mg IV followed by hydrocortisone 50 mg IV every 6 hours; this regimen can be subsequently tapered depending on the clinical course (198). For baseline doses of corticosteroids, glucocorticoid replacement with 15 to 25 mg of hydrocortisone PO daily in divided doses provides adequate replacement for most patients with PAI (198). Mineralocorticoid replacement with fludrocortisone can be helpful in patients with confirmed aldosterone deficiency to reduce salt craving and postural hypotension and prevent hyponatremia and hyperkalemia. Starting doses of fludrocortisone of 50 to 100 μg PO daily in adults can be used and titrated based on symptoms and laboratory monitoring of electrolyte levels (198).

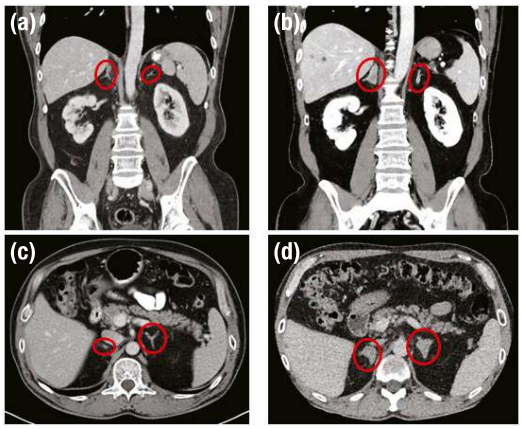

Figure 6. ICPi-related adrenalitis. A 59-year-old man with stage IIIB/IV malignant melanoma was started on ipilimumab therapy. (A) Coronal view and (C) axial view. Baseline abdominal CT 1 mo prior to ipilimumab initiation showed normal-appearing bilateral adrenal glands (red ovals). Six d after his first ipilimumab dose, he developed a pruritic maculopapular rash attributed to ipilimumab. He was treated with topical triamcinolone and a 3-d course of methylprednisolone PO. Three wk after his second dose of ipilimumab, he presented to the emergency department with epigastric pain radiating to the back, nausea, and vomiting. (B) Coronal view and (D) axial view. Abdominal CT scan showed bilateral enlarged adrenal glands (red ovals) with preserved contours, consistent with adrenalitis; no other radiographic abnormalities were seen. ACTH and cortisol drawn at 0900 h were 38 pg/mL (reference range, 7.2 to 68 pg/mL) and 20.8 μg/dL (reference range, 6.0 to 18.4 μg/dL), respectively, and sodium and potassium levels were unremarkable. He was treated with prednisone 60 mg PO daily for concern for ICPi-related abdominal pain and was tapered over the course of several wk to 20 mg PO daily. Four wk after his presentation with abdominal pain, cosyntropin stimulation test for aldosterone showed no rise in aldosterone (<4.0 ng/dL at baseline; <4.0 ng/dL 60 min after cosyntropin 250 μg IV administration), concerning for PAI. He was started on fludrocortisone 100 μg PO daily. He also subsequently developed ipilimumab-related hypophysitis complicated by central hypothyroidism requiring levothyroxine supplementation; pituitary MRI confirmed new pituitary enlargement. Abdominal MRI 2 mo after his presentation of abdominal pain showed resolution of bilateral adrenal enlargement, with normal-appearing bilateral adrenal glands. He remains on replacement corticosteroid doses 3 mo after his presentation of abdominal pain. [© 2019 Illustration Presentation ENDOCRINE SOCIETY].

Counseling

In agreement with the Endocrine Society guidelines on PAI, we recommend that health care providers counsel all patients with adrenal insufficiency regarding sick day rules and stress-dose and emergency corticosteroid administration, instruct them to obtain medical alert gear (such as a bracelet or necklace) regarding adrenal insufficiency, and prescribe a kit with injectable high-dose corticosteroid for emergency use (198).

Patients with mineralocorticoid deficiency requiring fludrocortisone replacement should be counseled that the fludrocortisone dose may need to be increased in circumstances of increased salt loss, such as hotter ambient temperatures or exercise. Liberalizing salt intake in these circumstances may also help prevent symptoms of mineralocorticoid deficiency.

Prognosis

Long-term outcomes of ICPi-related PAI have not been reported. In our experience with two patients with ICPi-related PAI, both patients required long-term glucocorticoid and mineralocorticoid replacement.

Association Between irAEs Due to ICPi Therapy and Clinical Cancer Response

It has been theorized that the development of irAEs during ICPi therapy may be a positive predictor of response to treatment, as reduction of immune self-tolerance to the point of triggering irAEs may be associated with an enhanced ability of the immune system

to recognize and destroy cancer cells. The outcomes from several studies support this theory, as will be discussed later. However, research on this topic has produced mixed results, and it remains an area of active investigation. Specifically, little is known about the association between endocrine irAEs and clinical cancer response to ICPi therapy. We will first focus on what is known about the relationship between endocrine irAEs due to ICPi therapy and cancer survival and conclude by reviewing what is known more generally about irAEs and cancer outcomes.

ICPi-related hypophysitis and clinical cancer response

Faje *et al.* (155) studied 154 patients with metastatic melanoma treated with ipilimumab at a single institution. Ipilimumab-related hypophysitis was diagnosed in 17 patients (11%). Median survival in patients who developed ipilimumab-related hypophysitis was 19.4 months vs 8.8 months in those who did not develop hypophysitis ($P = 0.05$). This significant difference in survival persisted in an updated review of 228 patients with melanoma treated with ipilimumab at the original institution (median survival 21.4 vs 9.7 months, $P = 0.008$) (164).

ICPi-related thyroid dysfunction and clinical cancer response

Osorio *et al.* (208) studied the association of ICPi-related thyroid dysfunction and survival outcomes in 48 patients with advanced NSCLC treated with pembrolizumab as part of KEYNOTE-001 (NCT01295827). The study found that in patients treated with pembrolizumab, median OS was significantly longer in those who developed thyroid dysfunction than those without thyroid dysfunction [median 40 vs 14 months; hazard ratio (HR) 0.29; 95% CI, 0.09 to 0.94, $P = 0.029$]. Progression-free survival (PFS) was numerically but not statistically significantly longer in those who developed thyroid dysfunction than those without thyroid dysfunction (median 8 vs 2 months; HR, 0.58; 95% CI, 0.27 to 1.21, $P = 0.14$).

Other irAEs associated with ICPi therapy and clinical cancer response

The onset of vitiligo in particular has been shown to be associated with improved outcomes in melanoma with both ICPi and non-ICPi immunotherapy (277–279). More generally, the development of cutaneous irAEs (such as rash, pruritus, hypopigmentation, xerosis, keratosis, and facial erythema) was associated with significantly longer PFS in patients with melanoma treated with pembrolizumab (280).

Although two studies did not find a difference in cancer-related outcomes between patients who developed or did not develop irAEs with ICPi therapy (281, 282), several other studies have. Beck *et al.* (283) found that development of ipilimumab-related enterocolitis was associated with significantly higher objective tumor response rates in patients with metastatic melanoma or renal cell carcinoma. Downey *et al.* (195) found that development of ipilimumab-related irAEs was associated with a greater probability of objective antitumor response ($P = 0.0004$) in patients with metastatic melanoma; of the three patients who achieved complete responses, all of them developed severe irAEs.

It remains to be determined whether development of irAEs in specific organs correlates with different rates of response to ICPi therapy. Freeman-Keller *et al.* (284) found that patients treated with nivolumab for melanoma who developed any irAE had a statistically significant improvement in OS compared with those who did not ($P < 0.001$). However, subset analysis showed statistically significant OS differences with rash [$P = 0.001$ (HR, 0.423; 95% CI, 0.243 to 0.735)] and vitiligo [$P = 0.012$ (HR, 0.184; 95% CI, 0.036 to 0.94)] but not with endocrinopathies, colitis, or pneumonitis. Whether this finding is due to the specific ICPi agent, the underlying malignancy, the particular organ-related irAEs studied, or study limitations such as a relatively small sample size or its retrospective nature remains unclear.

In a prospective study of the association of irAEs and survival, Teraoka *et al.* (285) investigated 43 patients with advanced NSCLC treated with nivolumab. This association was assessed based on whether patients had developed irAEs by 2 weeks or 6 weeks after nivolumab initiation. The study found that PFS was significantly longer in patients who had developed irAEs by 2 weeks after treatment initiation compared with those who had not [6.4 months (95% CI, 2.5 to not reached) vs 1.5 months (95% CI, 1.2 to 2.3), $P = 0.01$]. A similar trend in improved PFS was observed in patients who had developed irAEs by 6 weeks after treatment initiation compared with those who had not [4.1 months (95% CI, 1.8 to not reached) vs 1.5 months (95% CI, 1.2 to 2.3 months), $P = 0.06$]. Additionally, patients who had developed irAEs by 2 weeks after treatment initiation had higher rates of objective response and disease control than those who had not (37% vs 17%, $P = 0.17$; 74% vs 29%, $P < 0.01$, respectively). A similar trend was observed in patients who had developed irAEs by 6 weeks compared with those who had not (objective response rate, 33% vs 13%, $P = 0.17$; disease control rate, 59% vs 31%, $P = 0.12$). Rash and pyrexia were the most common irAEs in this study, followed by diarrhea and increased hepatic enzyme levels. Interestingly, in this study, only one patient developed hyperthyroidism within 6 weeks after nivolumab initiation (a relatively low incidence of thyroid-related dysfunction by 6 weeks for nivolumab), and other endocrine irAEs such as hypophysitis, DM, and adrenal dysfunction were not reported in this cohort within 6 weeks after nivolumab initiation.

In summary, several studies suggest a positive association between the development of irAEs due to ICPi therapy and improvements in tumor response and survival. However, available studies are limited, particularly by sample size and by their retrospective nature, and further research needs to be conducted in this important area.

Future Directions

Further research in several key areas is needed to enhance our understanding and management of ICPi-related endocrinopathies. Additional studies are needed to clarify the mechanisms underlying the development of ICPi-related endocrinopathies, particularly for ICPi-related hypophysitis and thyroid dysfunction, given their relatively high incidence. Identifying risk factors that predispose to the development of ICPi-related endocrinopathies could help guide the selection of ICPi therapy and the frequency of monitoring for these irAEs. Regarding the management of ICPi-related endocrinopathies, research is needed on the role of corticosteroids in the treatment of ICPi-related endocrinopathies and the effects of corticosteroid treatment on both the outcome and resolution of ICPi-related endocrinopathies and on oncologic response.

The field of ICPi therapy in cancer treatment is expanding to include combining ICPi therapy with other therapies such as vaccines, oncolytic viruses, costimulatory antibodies, adoptive T-cell and chimeric antigen receptor T-cell therapy, targeted therapy, angiogenesis inhibition, radiation therapy, and chemotherapy (286). Whether these combinations will result in different rates and patterns of ICPi-related endocrinopathies remains to be determined.

Conclusion

ICPi therapy has provided a powerful and promising new tool in the treatment of cancer. However, it is associated with a variety of irAEs quite different from the adverse effects associated with conventional chemotherapy, radiation, and other cancer treatment modalities. ICPi-related hypophysitis and thyroid dysfunction are relatively common irAEs, and ICPi-related insulin-deficient DM and PAI may occur as well. These endocrinopathies may be life-threatening if not promptly recognized and treated. Patients and their families need to be educated regarding the symptoms and signs of ICPi-related endocrinopathies. Oncologists, endocrinologists, primary care providers, and other medical providers caring for patients on ICPi therapy need to be aware of the clinical manifestations, diagnosis, and management of ICPi-related endocrinopathies. Many of the hormone deficiencies associated with ICPi-related endocrinopathies may be permanent; however, hormone replacement is effective in the vast majority of cases. Effective communication and coordination between oncologists and endocrinologists can facilitate optimal management and outcomes for patients who develop ICPi-related endocrinopathies.

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Abbreviations

^{18}FDG-PET/CT, 18-fluorodeoxyglucose-positron emission tomography/CT; ADCC, antibody-dependent cell-mediated cytotoxicity; ADH, antidiuretic hormone; AITD, autoimmune thyroid disease; Akt, protein kinase B; APC, antigen-presenting cell; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DI, diabetes insipidus; DKA, diabetic ketoacidosis; DM, diabetes mellitus; FDA, Food and Drug Administration; HbA1c, hemoglobin A1c; HR, hazard ratio; IA2, islet antigen 2; ICPi, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; irAE, immune-related adverse event; mAb, monoclonal antibody; MHC, major histocompatibility complex; NOD, nonobese diabetic; NSCLC, nonsmall cell lung cancer; NTIS, nonthyroidal illness syndrome; OS, overall survival; PAI, primary adrenal insufficiency; PD-1, programmed death 1; PFS, progression-free survival; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PO, by mouth; RCT, randomized controlled trial; SNP, single nucleotide polymorphism; T1DM, type 1 diabetes mellitus; TCR, T-cell receptor; Tfh, follicular helper T; TFT, thyroid function test; TgAb, thyroglobulin antibody; TPO Ab, thyroperoxidase antibody; TRAb, thyrotropin receptor antibody; Treg, regulatory T-cell; TSI, thyroid-stimulating immunoglobulin; UTR, untranslated region.