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Immune checkpoint inhibitor-related endocrinopathies

Difei Lu, Ying Gao
Department of Endocrinology, Peking University First Hospital, Beijing 100034, China

BACKGROUND

Since the past 10 years, immune checkpoint inhibitors (ICIs), including programmed cell death protein-1 (PD-1) inhibitors, programmed death-ligand 1 (PD-L1) inhibitors, and cytotoxic T cell-associated protein-4 (CTLA-4) inhibitors, have become a remarkable therapeutic improvement for patients with advanced malignancy.[1] Along with their antitumor process, the overactivated immune cells could result in autoimmune damage in various organs including skin, gastrointestinal, pulmonary, cardiac, renal, and endocrine systems, which are called immune-related adverse events (irAEs).[2] ICI-related endocrinopathies are most common. ICI-related thyroid dysfunction (ICI-TD) is the leading subtype and hypophysitis is ranked second; these are followed by ICI-related insulin-deficient diabetes mellitus (DM), primary adrenal insufficiency (PAI), and autoimmune polyendocrine syndrome (APS), which have been described in several case reports.[3] Although most subtypes of endocrinopathies were mild, rare cases of thyrotoxic crisis, myxedema crisis, and adrenal crisis induced by ICI have also been reported. Therefore, comprehensive data of ICI-related endocrinopathies is critical for clinicians. In the present study, we aim to give new insights about ICI-related endocrinopathies based on recent clinical evidence and guidelines.

UNDERLYING MECHANISM OF ICI-RELATED ENDOCRINOPATHIES

The detailed mechanism of ICI-related endocrinopathies remains unclear. There is slight difference of T cell modulation among the three kinds of ICIs. CTLA-4 is expressed after T cell activation and it downregulates T cell activation by competitive inhibition of co-stimulation of CD28 with B7 ligands.[4] Also, PD-1 conducts a negative costimulatory function through combination with PD-L1, and thus, it leads to attenuated T cell activation and tumor immune escape.[5] In patients with ICI-TDs, presence of significantly increased $CD4^+PD1^+$ T lymphocytes was proved by flow cytometry of thyroid fine-needle aspiration.[6] Furthermore, in rodent models, it was revealed that cytotoxic memory $CD4^+$ T cell was activated by PD-1 antibody and led to anti-PD-1 therapy-related destructive thyroiditis.[7] The pituitary glands at autopsy of six patients with CTLA-4 blockade-induced hypophysitis proved the expression of CTLA-4 and extensive destruction after immune reactions.[8] Another study proved that treatment with anti-CTLA-4 antibody precipitated pituitary cells' destruction via classic complement pathway.[9] Similar to hypophysitis, a provocative hypothesis of the pathogenesis of ICI-related diabetes was that PD-L1 was highly expressed by pancreatic β cells that were resistant to T cell-mediated apoptosis.[10] Therefore, PD-L1 inhibitors brought about immune response in the β cells surviving for a long term and resulted in rapid-onset fulminant diabetes.[10] However, the mechanism of PAI is still unknown. The different local expression of immune molecules in each affected endocrine gland may determine the varied impairment partly induced by each subtype of ICIs (Table 1).

There is a lack of study on the biopsy of ICI-related endocrinopathies. Aside from the pathology study of hypophysitis mentioned above, a case report of the

Address for Correspondence:
Prof. Ying Gao, MD, Department of Endocrinology, Peking University First Hospital, No. 8 Xi Shi Ku Street, Xicheng District, Beijing 100034, China.
E-mail: bjgaoying@yahoo.com

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Table 1: The mechanism and predisposition of endocrinopathies induced by different subtypes of ICIs

Subtype	Autoimmune mediated?	Mechanistic insights	HLA associated?	Most common induced ICIs	Insights into susceptibility of endocrine AEs
Thyroid dysfunction[6,7,11,15,20]	Yes	Increased $CD4^+PD1^+$ T lymphocytes in FNA. Activated cytotoxic memory $CD4^+$ T cells in PD-1 inhibitor-induced destructive thyroiditis	No	PD-1 inhibitor	Combination therapy increased the risk of ICI-related thyroiditis
Hypophysitis[8,9,20]	Yes	CTLA-4 expression in pituitary cells. Activation of classic complement pathway by anti-CTLA-4 antibody during pituitary cell destruction	Probable	CTLA-4 inhibitor	Dose-dependent manner was seen in the incidence of CTLA-4 inhibitor-induced hypophysitis
DM[10,12,27]	Yes	PD-L1 upregulation on islet β cells	Strongly associated	PD-1 or PD-L1 inhibitor	Upregulation of PD-L1 on pancreatic β cells
PAI[30]	Yes	Insufficient evidence	No	PD-1 inhibitor	Insufficient evidence
APS[33]	Yes	Insufficient evidence	Insufficient evidence	PD-1 inhibitor monotherapy in 60.9% cases	Insufficient evidence

DM: diabetes mellitus; PAI: primary adrenal insufficiency; APS: autoimmune polyendocrine syndrome; FNA: fine-needle aspiration; HLA: human leukocyte antigen; PD-1: programmed cell death protein-1; PD-L1: programmed death-ligand 1; CTLA-4: cytotoxic T cell-associated protein-4; ICIs: immune checkpoint inhibitors.

pathological findings of ICI-related thyroiditis revealed distinguishing features including clusters of necrotic cells and lymphocytes' infiltration.[11] The injury of endocrine glands by ICIs may provide a natural model of immune damage to endocrine organs, which would help investigate the underlying mechanisms of autoimmune endocrine disease from a novel perspective.

PREDISPOSITION OF ENDOCRINE AES OF DIFFERENT SUBTYPES OF ICIS

The heterogeneity in different subtypes of ICI-related endocrinopathies is found in the three kinds of immunotherapy (Table 1). Genetic factors showed a predisposition in DM and APS induced by ICIs.[12] Human leukocyte antigen (HLA) DR4 (51.3%) was predominantly seen in patients with ICI-related diabetes,[12] while it was reported that HLA-DR and HLA-DQ were associated with fulminant type 1 diabetes or type 1 diabetes with positive glutamate decarboxylase (GAD) antibody.[13-14] Immunotherapy may be a contributing factor in the population with predisposing HLA genotype and accelerated disease progression in ICI-related DM. In contrast, no predominance of HLA was discovered in patients with ICI-TDs.[15]

Other predisposing factors of irAEs include higher dose of CTLA-4 blockade, combined therapy of ICIs, and preexisting autoimmune diseases.[16] A multicenter observational study found elevated incidence of irAEs in patients with preexisting systemic autoimmune diseases, while the risk of grade 3/4 irAEs was insignificantly different.[17] A future research direction is to investigate whether patients with preexisting endocrine autoimmune diseases, such as autoimmune thyroid diseases, are predisposed to ICI-related endocrinopathies and safety of immunotherapy in them.

SEVERITY OF ICI-RELATED ENDOCRINOPATHIES

ICI-related endocrinopathies show mostly mild presentation based on the Common Terminology Criteria for Adverse Events (CTCAE) criteria,[18] and the incidence of grade 3/4 irAEs in endocrine organs does not exceed 1%.[12] In a retrospective study using the World Health Organization (WHO) adverse drug reaction database, VigiBase, the incidence of ICI-TDs in grade 3/4 was 0.68%, with the affected patients showing major or fatal consequences.[19] To date, there is still a lack of real-world evidence from large populations.

CLINICAL MANIFESTATIONS OF ICI-RELATED ENDOCRINOPATHIES

The incidence and manifestations of each ICI-related endocrinopathy are listed in Table 2.[20-33] ICI-induced APS is even rare. In our previous study, the likelihood of APS in patients on combination therapy of anti-CTLA-4 and anti-PD-1 increased onefold than in patients on PD-1 inhibitors and fourfold than in those on PD-L1 inhibitors.[32]

Table 2: Clinical manifestations of ICI-related endocrinopathies

Endocrinopathies	Incidence (%)	Gender predominance	Classic manifestations	Onset time after ICI initiation
ICI-TDs[20-23]	2.60–6.07	Female predominance	Transient thyrotoxicosis preceding hypothyroidism Graves' disease with 50% negative TRAb 11 cases of thyrotoxic crisis and one case of myxedema were reported	Thyrotoxicosis at 5.3 weeks Hypothyroidism at 10.4 weeks
Hypophysitis[20,24-26]	3.2–6.4	Male:female ratio 4:1	Symptoms included headache and presentations of pituitary hormone dysfunction Radiologic sign was pituitary stalk enlargement Secondary adrenal insufficiency was most common, followed by central hypothyroidism, hypogonadotropic hypogonadism, and GH deficiency. Diabetes insipidus rarely occurs	Several weeks to 3 months
DM[16,27-29]	1.18–2.60	No gender predominance	Rapid onset of hyperglycemia and progression of insulin deficiency. DKA occurrence rate was 70% In most cases at diagnosis, glucose level exceeded 18 mmol/L, with HbA_{1c} less than 8.0% and random C-peptide less than 0.1 ng/mL 50% cases displayed positive autoimmune diabetic antibodies CT scan or MR imaging showed pancreatic enlargement followed by progressive pancreatic atrophy Slightly elevated amylase levels	At 1 week to 12 months, median onset time was 3 months
PAI[30,31]	0.9	The proportion of males was 58.1%	Low cortisol level and elevated ACTH level, severe hyponatremia, hyperkalemia, and reduced aldosterone level Imaging showed bilateral enlargement of adrenal glands Positive 21-hydroxylase adrenal cortex antibody was reported	Not enough evidence
APS[33]	Not enough evidence	Not enough evidence	More than one of the above diseases co-occurred with manifestations of each disease	Not enough evidence

ICIs: immune checkpoint inhibitors; ICI-TDs: ICI-related thyroid dysfunction; DM: diabetes mellitus; PAI: primary adrenal insufficiency; APS: autoimmune polyendocrine syndrome; TRAb: thyroid-stimulating hormone receptor antibody; GH: growth hormone; DKA: diabetic ketoacidosis; PD-1: programmed cell death protein-1; PD-L1: programmed death-ligand 1; CTLA-4: cytotoxic T cell-associated protein-4; CT: computed tomography; MR: magnetic resonance

DEBATING ON THE TREATMENT OF ICI-RELATED ENDOCRINOPATHIES

For cases of all endocrinopathies in CTCAE grade 1, immunotherapy could be continued during the diagnosis and management of the endocrinopathies. In the case of CTCAE grade 2–4, immunotherapy should be discontinued until the endocrinopathy is managed by standard treatment.[12] Importantly, clinicians are confused about the safety of restarting immunotherapy in patients who have recovered from grade 4 ICI-related endocrinopathies. For grade 3/4 hypophysitis and grade 4 ICI-TDs, the decision of restarting immunotherapy after the endocrinopathy is treated or permanently discontinuing ICI therapy is under debate.[2,34] It was proved that the risk of both initial irAE and other kinds of new-onset irAE was not increased after resuming PD-1 inhibitors in patients who recovered from severe irAEs.[35] Unfortunately, no similar study focusing on grade 4 ICI-related endocrinopathies was conducted to prove the safety of restarting immunotherapy. Study concerning the clinical outcomes of restarting immunotherapy in patients who recovered from grade 3/4 endocrine AEs is of great importance for taking a clinical decision for patients with advanced malignancy.

For the management of insufficiency of endocrine function, replacement therapy is recommended. The need of lifelong replacement varied in endocrine glands and studies. Among ICI-TDs, a possibility of remission was seen in overt hypothyroidism after thyrotoxicosis in ICI-induced silent thyroiditis. However, damage to thyroid function may continue to reach an irreversible situation. since it is not recommended to discontinue ICI in patients with grade 1/2 ICI-TDs. Thus, in nearly half of the cases, de novo hypothyroidism induced by ICIs needed lifelong replacement therapy.[36] In ICI-related hypophysitis, the inflammatory mass of pituitary resolved in most cases, while hormone deficiency persisted.[37] The spontaneous recovery rate of central hypothyroidism and hypogonadotropic hypogonadism was observed to be 30%–60%,[23] while ICI-related central adrenal insufficiency persisted in all cases, which should be managed with lifelong corticosteroid replacement. There is a rapid progression of deficiency of endogenous insulin secretion

in ICI-related DM. Due to permanently compromised insulin secretion, lifelong insulin therapy is needed even in patients with preexisting type 2 diabetes.[28] Likewise, lifelong glucocorticoid replacement in ICI-related PAI is urgent, and it should be given promptly to avoid adrenal crisis.[37]

Endocrine damage induced by ICIs on high-dose steroid treatment is under debate. In patients with grade 4 hypophysitis, high-dose steroids (prednisone/methylprednisolone 1 mg/kg/d) are recommended to relieve acute severe symptoms until the symptoms resolve in an average 1–2 weeks and taper rapidly to physiologic replacement dose.[38] However, a retrospective study revealed that systemic high-dose corticosteroid (prednisone 40–100 mg/d) treatment did not improve the outcome of ipilimumab-related hypophysitis.[39] To the best of our knowledge, no systematic study regarding the efficacy of high-dose glucocorticoids to suppress the autoimmune damage on endocrine organs on the outcome or reversal of grade 4 ICI-related endocrinopathies has proved, along with the possible higher risk of tumor progression in the treatment with high-dose glucocorticoids due to the decreased antitumor efficacy of immunotherapy.[16] Therefore, in case of ICI-related endocrine crisis such as thyrotoxic crisis, myxedema, or adrenal crisis,[38] treatment with high-dose steroids was recommended for the purpose of relieving acute symptoms. Whether short-term treatment with high-dose steroids in endocrine crisis increased the risk of tumor progression calls for real-world evidence.

IMPACT ON PROGNOSIS OF ICI-RELATED ENDOCRINOPATHIES

Among all ICI-related endocrinopathies, the prognosis of ICI-related PAI was poor. The risk of severe clinical outcomes in ICI-related PAI was over 90%, and the mortality rate was up to 7.3%.[30]

Interestingly, in tumor prognosis, endocrine adverse events are not always linked to adverse outcomes. Kim *et al.*[40] found a longer OS and progression-free survival (PFS) in 58 patients who developed ICI-TDs with stage IV non-small-cell lung cancer (NSCLC) under PD-1 blockade. Researchers believed that the development of irAEs could partly reflect the antitumor efficacy in patients on ICI regimens, though it is accompanied with a proportion of immortal time bias.[41] However, our data from FAERS database concluded differently. In patients on ICI therapy with adverse events, the immune-related endocrinopathies, including ICI-TDs and other accompanying endocrinopathies, were positively associated with the risk of severe clinical outcomes comprising hospitalization, disabled or life-threatening situations, while they were negatively related to the risk of death.[32] Therefore, irAEs of endocrine organs are critical clues for clinicians to pay attention to. Once the endocrine function alters and endocrinologic irAEs happen, oncologists or endocrinologists ought to start administering replacement therapy or other management in time to avoid serious clinical outcomes.

NEW INSIGHTS INTO THE APPLICATION OF ICIS ON MALIGNANCIES OF ENDOCRINE SYSTEM

Evidence has accumulated on the application of ICIs in pulmonary combined large cell neuroendocrine carcinoma (LCNEC), anaplastic thyroid cancer (ATC), and advanced adrenocortical carcinoma (ACC),[42-45] which displayed aggressive behavior and poor prognosis. PD-L1 had an increased proportion of tumoral expression on ATC,[43] and PD-1 inhibitor pembrolizumab was a promising choice of treatment in ATC, based on small studies.[42] Well-designed randomized controlled trials (RCTs) are still in need to provide stronger evidence on immunotherapy in the above malignancies of endocrine systems.

PERSPECTIVES

The wide application of ICIs has brought about a novel spectrum of immune-related endocrinopathies in a significant number of patients. Awareness of the heterogeneity in manifestations of ICI-related endocrinopathies is crucial to guide endocrinologists and oncologists. A main dilemma is how to treat our patients properly with ICIs with the purpose of avoiding AEs and benefiting from antitumor effect. Additionally, ICIs-AE might be a model of immune imbalance for the research of autoimmune diseases.

Conflict of Interest

All authors declare that they have no conflict of interests.

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