Chapter 29

ENDOCRINE COMPLICATIONS OF IMMUNE CHECKPOINT İNHIBITOR THERAPY

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INTRODUCTION:

Immune checkpoints are small molecules located on the surface of immune cells that take part in regulating immune response (1). Immune checkpoint blockade inhibits immunity regulators such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1) or its ligand programmed death ligand 1 (PD-L1), augmenting anti-tumor immunity. Various immune checkpoint inhibitors (ICPis) are shown to increase overall survival for a variety of cancer patients and have been approved by Food and Drug Administration (FDA) (2). Currently available ICPis include Anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab, pembrolizumab) and anti-PD-L1 (atezolizumab, avelumab, durvalumab).

ICPis may cause inflammatory side effects, which are frequently named as immune-related adverse events, by increasing the activity of the immune system. Immune-related adverse events (irAE) most commonly involve the gastrointestinal system, endocrine system, skin and liver, although involvement of any organ system is possible (3). Immure-related adverse events are the most commonly-encountered complications of ICPi therapy and endocrinopathies are among the most prevalent irAEs.

The most common ICPi-associated endocrinopathies include hypophysitis, thyroid dysfunction, insulin-deficient diabetes mellitus (DM) and primary adrenal insufficiency (PAI). Some endocrinopathies are more common with certain ICPis. Hypophysitis is relatively more frequent with ipilimumab, an antiCTLA-4. Thyroid dysfunction is more commonly observed with antiPD-1 agents nivolumab and pembrolizumab. Combined use of these drugs further increases the risk of ICPi-associated endocrinopathies (4). Mortality due to immune-related adverse events is rare but myocarditis, pneumonia, colitis and neurologic event may be fatal (2).

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promptly with insulin (12). Patients receiving ICPi therapy and their families should be informed about the signs and symptoms of hyperglycemia and DKA. DKA is a life-threatening complication of ICPi-associated DM. Early diagnosis of new-onset hyperglycemia, insulin treatment and starting fluid resuscitation immediately can prevent progression to DKA. ICPi-associated DM can cause total destruction of insulin secretion capacity and result in long-term insulin requirement (27). Multidose insulin therapy with basal-bolus insulin regimen is the basis of treatment.

ICPI-RELATED PRIMARY ADRENAL INSUFFICIENCY

Primary adrenal insufficiency (PAI) is a rare irAE associated with ICPi therapy (28). Randomized clinical studies report PAI incidence to be 0.7% in patients treated with ICPis (4). PAI is reported with ipilimumab, nivolumab and pembrolizumab therapies (28-31). High levels of ACTH and low levels of cortisol are found in PAI. Cosyntropin stimulation test yields inadequate increase in cortisol levels. Low levels of aldosterone and high levels of renin can also be observed and hyperkalemia and hyponatremia may accompany the clinical presentation (32). PAI should be distinguished from central adrenal insufficiency. Unlike central adrenal insufficiency, PAI requires mineralocorticoid replacement in addition to glucocorticoid replacement.

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