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PROCEEDINGS ABSTRACT

Endocrinopathies associated with immune checkpoint inhibitors: incidence, clinical presentation, and management

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Immune checkpoint inhibitors (CPIs) have fundamentally shifted the oncology landscape by blocking inhibitory pathways that tumours exploit to evade the immune system. By targeting proteins such as the cytotoxic T-lymphocyte associated protein 4 (CTLA-4; e.g., ipilimumab), the programmed cell death protein 1 (PD-1; e.g., pembrolizumab and nivolumab), and the programmed death-ligand 1 (PD-L1; e.g., atezolizumab), these therapies unleash T-cell activity against malignant cells. However, this non-specific immune activation frequently leads to immune-related adverse events (irAEs). Endocrinopathies are among the most common and distinct irAEs, characterised by their often sudden onset and high likelihood of becoming permanent, thereby requiring vigilant pharmacological intervention and lifelong replacement therapy. The mechanisms of the CPI-induced endocrinopathies are distinct from those of traditional autoimmune diseases and vary by drug class. While thyroid dysfunction is the most common endocrinopathy across all CPIs, hypophysitis is the "signature" toxicity of CTLA-4 blockade (e.g., ipilimumab). Hypophysitis is significantly less common with PD-1 / PD-L1 monotherapy. In contrast, anti-PD-1 / PD-L1 therapies are more frequently associated with thyroiditis and type 1 diabetes mellitus (CPI-DM). Combination of anti-CTLA-4 with anti-PD-1 treatments significantly increases the risk of hypophysitis and multi-gland involvement due to a synergistic immune activation at multiple checkpoints. The clinical presentation of hypophysitis is variable, but more commonly includes central adrenal insufficiency. Thyroid dysfunction is the most frequent endocrine irAE. It often manifests as a transient thyrotoxic phase due to destructive thyroiditis, followed by a rapid transition to permanent hypothyroidism. Insulin-deficient diabetes is a rare (~1%) medical emergency, often presenting with severe hyperglycaemia and / or diabetic ketoacidosis. It is characterised by rapid β-cell destruction. Patients usually present with low or undetectable C-peptide levels and, in 30%–50% of the cases, with diabetes auto-antibodies. Finally, primary adrenal insufficiency is rare, but life-threatening; it is distinguished from hypophysitis by the presence of mineralocorticoid deficiency (hyperkalaemia / hyponatraemia). As far as the diagnostic work-up and monitoring are concerned, vigilant screening is mandatory because symptoms like fatigue and nausea are non-specific and can easily be attributed to the underlying cancer. The baseline testing of thyroid-stimulating hormone, free thyroxine, and morning cortisol levels is essential. Throughout treatment, clinicians should monitor thyroid function and blood glucose levels at every infusion cycle. In cases of suspected hypophysitis, MRI may show pituitary enlargement, but treatment should not be delayed for

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imaging if the patient is haemodynamically unstable. A critical distinction in managing endocrine irAEs compared to other organ-specific toxicities (such as colitis or pneumonitis) is the role of immunosuppression. While high-dose glucocorticoids are used to dampen inflammation in other organs, they rarely reverse endocrine gland destruction. Consequently, management shifts from "curing" the inflammation to hormone replacement. A vital pharmacological pearl is the sequence of replacement: adrenal insufficiency must be treated with hydrocortisone before initiating levothyroxine to prevent the precipitation of an acute adrenal crisis due to increased metabolic clearance of cortisol. For CPI-DM, insulin is the only viable treatment; oral hypoglycaemics are ineffective due to the absolute insulin deficiency. In conclusion, as CPI use becomes standard across more cancer types, healthcare providers must recognise that endocrine toxicities are unique "side effects" that persist long after the drug is discontinued. Patient education on the permanent nature of these conditions is paramount for the prevention of mortality while maintaining the oncological benefits of immunotherapy.

Keywords

cancer; endocrinopathies; immune checkpoint inhibitors; immune-related adverse events; toxicities

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Conflicts of interest statement

None to declare.

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