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Primary adrenal insufficiency induced by immune checkpoint inhibitors: Biological, clinical, and radiological aspects

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ABSTRACT

Immune checkpoint inhibitors (ICI) have become a cornerstone in medical oncology, continually evolving therapeutic strategies and applications. These monoclonal antibodies, designed to enhance immune responses, have revealed a spectrum of immune-related adverse events (irAEs). While many irAEs exhibit favorable responses to corticosteroid or immunosuppressive therapy, most ICI-related endocrinopathies necessitate lifelong replacement therapy and pose significant clinical challenges. Adrenal insufficiency (AI), a noteworthy endocrine irAE, can manifest as primary AI (PAI) or secondary AI (SAI), resulting from adrenal or pituitary gland dysfunction, respectively. ICI-induced AI, albeit relatively infrequent, occurs in 1%–2% of patients receiving single-agent anti-Programmed Death-1/Programmed Death-Ligand 1 (PD-1/PD-L1) or Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) therapies and in a higher range of 4%–9% when ICIs are used in combinations. Recognizing and addressing ICI-induced PAI is crucial, as it often presents with acute and potentially life-threatening symptoms, especially considering the expanding use of ICI therapy. This review provides an updated overview of ICI-induced PAI, exploring its clinical, diagnostic, and radiological aspects.

Introduction

Treatment with immune checkpoint inhibitors (ICI) has become one of the pillars of medical oncology, with continuous developments regarding new therapeutics and indications. ICIs are monoclonal antibodies targeting proteins involved in activating the immune response. However, ICI-induced immune system activation can lead to a loss of immune system regulation, resulting in unwanted adverse events (AEs). Endocrinopathies have been commonly recognized among immune-related adverse events (irAEs) [1]. Hypophysitis, thyroid dysfunction, type 1 diabetes mellitus (T1DM), central diabetes insipidus, and adrenal insufficiency (AI) are the principal ICI-induced endocrine irAEs [2].

In contrast to many irAEs that often respond to treatment with corticosteroids or immunosuppressive agents, most ICI-related endocrinopathies require lifelong replacement therapy and may be considered more consequential adverse events of ICIs. In addition, endocrine irAEs are more prevalent, with an incidence of up to 16% depending on the irAE and the treatment received based on two meta-analyses [3,4].

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AI is an endocrine irAE caused either by dysfunction of the adrenal glands, termed primary AI (PAI) or by dysfunction of the pituitary gland, termed secondary AI (SAI). ICI-induced AI is reported in 1-2% of patients treated with single-agent anti-Programmed Death-1/Programmed Death-Ligand 1 (PD-1 / PD-L1) or Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) therapies and is estimated to occur at a rate of 4%–9% in patients treated with combinations of ICIs [3–5].

Despite the relative rarity of ICI-induced PAI, due to the growing number of patients being treated with ICI therapy, recognition and adequate treatment of endocrine irAEs will become increasingly relevant. Especially, since this condition presents frequently with acute symptoms and may be life-threatening if not recognized in time. Therefore, the clinical care team should be aware of this irAE and the required diagnostic work-up and treatment. Although diagnostic modalities for PAI outside the scope of ICI are well documented, these remain mostly undescribed for ICI-induced PAI. Here, we aim to provide an overview of ICI-induced primary adrenal insufficiency based on current literature and report the radiological findings of a patient with ICI-induced PAI.

Function and dysfunction of the adrenal glands

The adrenal glands are paired organs located at the superior pole of each kidney in the retroperitoneal space. These endocrine glands comprise two embryologically and functionally distinct parts: the centrally located medulla and the peripherally located cortex, comprising approximately 10% and 90% of the normal adrenal mass. The medulla secretes hormones such as adrenaline and noradrenaline. The cortex is divided into three zones: the zona glomerulosa (10%), responsible for the synthesis and secretion of mineralocorticoids (aldosterone), the zona fasciculata (70%), mainly responsible for the synthesis and secretion of glucocorticoids and the zona reticularis (20%), mainly responsible for the synthesis and secretion of adrenal androgens. The zona fasciculata and zona reticularis are under the control of the adrenocorticotropic hormone (ACTH), whose release is stimulated by the pituitary corticotropin-releasing hormone (CRH). The kidneys primarily regulate the renin-angiotensin-aldosterone system and help regulate adrenal aldosterone production.

In Addison's disease, a dysfunction of the adrenal glands leads to PAI with decreased glucocorticoid production with or without mineralocorticoid hormones. ACTH levels are typically increased, due to absent inhibition of the pituitary gland by normal cortisol levels. PAI is a rare, potentially fatal disease that requires hormone replacement. Outside of the scope of ICI therapy, the incidence of PAI ranges from 10 to 20 per 100,000 individuals [6], with a higher incidence in the third decade of life, more often diagnosed in females, and a higher frequency in subjects affected by other autoimmune diseases [7,8]. An autoimmune etiology accounts for approximately 90% of PAI cases of non-genetic origin [9]. PAI may also present as part of an autoimmune polyendocrine syndrome (APS), in rare cases caused by inherited dysfunction in the autoimmune regulator gene (APS-1) or presenting as combination of two of the following endocrinopathies: PAI, T1DM and autoimmune thyroid disease (APS-2) [10]. Other causes of PAI include surgery, infections (eg, herpes simplex 1 virus, cytomegalovirus, HIV, adenovirus), bilateral adrenal metastases, infiltrative diseases, hemorrhages, infarction, and drugs [11,12]. Additionally, the growing use of ICIs has increased, and will further increase, the number of patients with therapy induced PAI.

Immune checkpoint inhibitor-induced adrenal insufficiency

ICI-induced adrenalitis leading to PAI is a rare entity. A systematic review by *Shi* et al. [13], published in 2020, identified this complication in only 15 case reports. As mentioned, ICI-induced AI is observed in 1%-2% and estimated in 4%–9% of patients after treatment with anti-PD-1 monotherapy or anti-PD-1 plus anti-CTLA-4 combination treatment, respectively [3–5]. Incidence of AI may vary depending on immunotherapy regimen and malignancy, although differences per malignancy may partly be explained by the amount of previous treatment lines before first immunotherapy is started. Importantly, the mentioned incidences of ICI-induced AI may not accurately reflect the incidence of PAI, as most clinical trials reporting ICI-induced AI as an adverse event do not discriminate between PAI and SAI [14,15]. In an analysis of VigiBase records of PAI, only 10% of reported ICI-induced PAI cases were confirmed as definite PAI, supporting the hypothesis that the actual prevalence of PAI may be lower [16]. Indeed, two monocenter retrospective analyses reported extremely low incidences of ICI-induced PAI, with 0 out of 76 patients (0%) and 2 out of 160 patients (1.3%) with ICI-induced AI identified as PAI cases, resulting in an estimated risk for PAI of $<$0.1% upon treatment with ICI [5,14]. Although rare, ICI-induced PAI may also present as APS-2, combined with ICI-induced type I diabetes and/or thyroid disease [17].

The median time to onset of ICI-related AI appears to be variable; a median onset at 10 weeks after the start of ICI has been reported [18], as well as 2.5–4.3 months after start of ICI, varying depending on the immunotherapy used [19]. It can also occur later, even after the end of treatment with ICIs [20]. In addition, it should be considered that not all trials monitor cortisol levels, which could result in a delay in diagnosis. Knowledge about the etiology underlying the pathogenesis of adrenal gland dysfunctions in the course of ICI-treatment is still poor, probably due to its low incidence, and the pathophysiological mechanism that remains unknown.

In patients with autoimmune adrenalitis, not associated with ICIs, autoantibodies against the adrenal cortex (ACA) and adrenal 21-β-hydroxylase are present in over 90% [21]; case-reports of ICI-induced PAI with positive 21-hydroxylase antibodies have been described [20,22]. According to some authors, the definitive character of the AI described in ICI is consistent with the autoimmune destruction of the adrenal glands mediated by both T-cells and other cells of the immune system [15,23].

Clinical manifestations and diagnostics

From a clinical point of view, the adrenal manifestations observed with ICI-induced PAI are similar to those observed in Addison's disease. The acute form often presents as a critical state (adrenal crisis), while the chronic ones can be more insidious. In the acute form, particularly in the case of an adrenal crisis, anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, and confusion may be present; laboratory data may show hyponatremia, hyperkalemia, hypercalcemia, hypoglycemia, and sometimes eosinophilia [24]. In the chronic form, patients mainly complain of fatigue (≈90%), weight loss (≈70%), nausea, vomiting, abdominal pain (≈55%) and muscle and joint pain (≈38%). In addition, hypotension, hyponatremia, hyperkalemia, hypercalcemia and hyperchloremia, acidosis, mild normocytic anemia, lymphocytosis, and eosinophilia may coexist [25]. The laboratory finding of hyponatremia is present in 90% of new-onset cases. However, the classic combination of hyponatremia and hyperkalemia is an unreliable indicator to formulate the diagnosis as sodium values can only be marginally reduced, while potassium levels are increased in only 50% of patients [26]. Anemia, mild eosinophilia, lymphocytosis, and increased hepatic transaminases may also be observed [27]; more rarely in adult patients, hypoglycemia up to hypoglycemic coma may occur. Androgen deficiency can lead to muscle weakness, fatigue, and decreased libido.

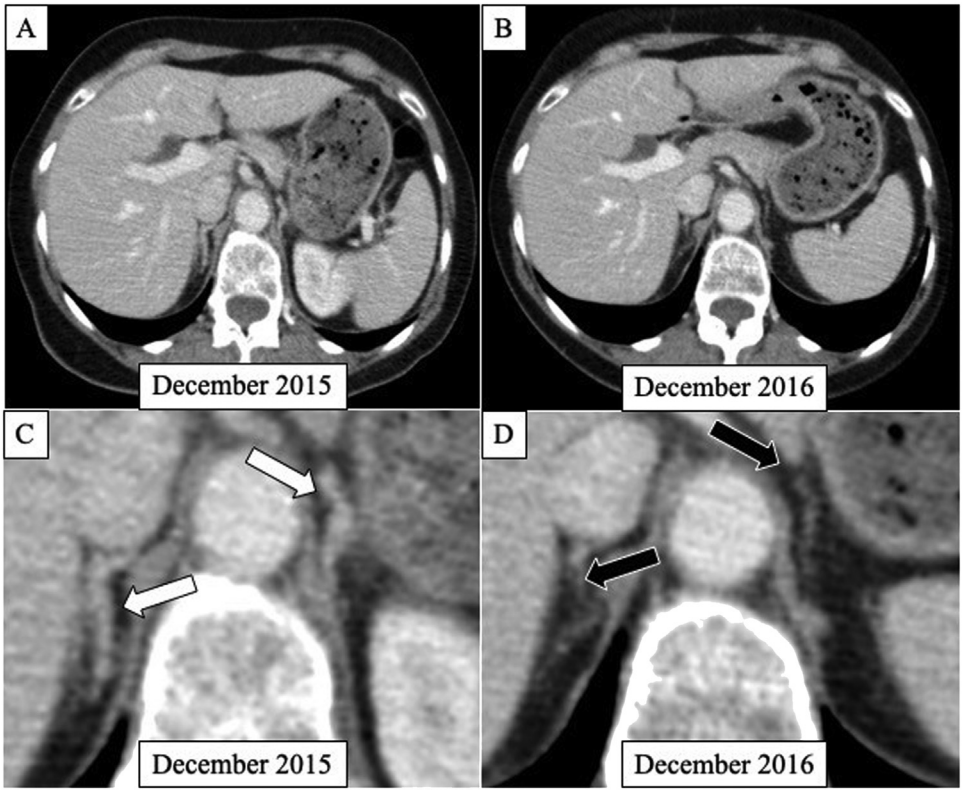

Fig. 1. A 66-year-old woman diagnosed with resectable stage III melanoma was treated with anti-PD-1/anti-CTLA4 combination therapy beginning in November 2015. Thirty-eight days after the start of the therapy, the patient started to experience nausea, fatigue, and anorexia progressively, and laboratory analysis revealed increased ACTH levels (976 ng/L), decreased cortisol level (0.06 μmol/L), and hyponatremia, and the diagnosis of PAI was made. *Following this diagnosis, the patient began corticosteroid replacement therapy with hydrocortisone, later partly replaced by fludrocortisone.* A contrast-enhanced CT scan obtained three days after PAI diagnosis (A, with details in C) showed normal adrenal glands (white arrows). A follow-up CT scan performed 1-year later, in December 2016 (B, with details in D), showed atrophy of both the adrenal glands (black arrows) without mass-like lesions and/or calcifications.

Differential diagnoses for ICI-induced PAI include conditions that may mimic the clinical presentation of adrenal crisis, such as sepsis, and alternative etiologies for adrenal gland dysfunction.

Ultimately, AI is diagnosed based on decreased morning cortisol serum levels, tested in combination with ACTH, with PAI being characterized by high ACTH levels [23,28,29]. A synacthen test can be performed to differentiate between primary and secondary etiology or to confirm an indeterminate diagnosis of AI, by administering 250 µg synthetic ACTH, which results in cortisol release ($\geq$ 500 nmol/L in serum after 30–60 minutes) in case of SAI and which will result in inadequate cortisol levels ($<$500 nmol/L) in PAI [30]. Of note, in case of iatrogenic AI due to long-term corticosteroid use, the adrenals may also produce inadequate levels of cortisol upon stimulation, complicating final diagnosis [28]. ICI-induced secondary AI mostly leads to isolated hypocortisolism due to ACTH deficiency, with mineralocorticoid production often remaining intact. The presence of hyperkalemia may, therefore, provides a clue towards the etiology of the condition.

Aside from cortisol and ACTH testing, both ESMO and ASCO guidelines recommend metabolic lab testing, including sodium, potassium, and glucose in patients with suspected AI. Additionally, in case of suspected SAI, it is advised to test the additional hormonal axes of the pituitary gland and to consider MRI of the brain to exclude hypophysitis [28,29].

As regards monitoring patients receiving ICIs, periodic determinations of cortisol and ACTH can be useful for identifying AI secondary to autoimmune adrenalitis or hypophysitis. Given the higher incidence of these manifestations in patients treated with anti-CTLA-4 alone or combinations of ICIs, it may be reasonable to propose an initial evaluation and serial monitoring of cortisol and ACTH, only in patients treated with immunotherapy regimens containing anti-CTLA-4.

Radiological assessment

The diagnosis of PAI is usually based on clinical signs and symptoms and confirmed by laboratory tests [31]. The role of radiologic investigations such as computed tomography (CT) and magnetic resonance imaging (MRI) is limited, although it may be supportive for the diagnosis, for example in the chronic phase [32–34]. Additionally, the ASCO guideline recommends CT imaging of the adrenals in case of PAI to rule out adrenal metastases or hemorrhage [28]. In patients with PAI, outside the scope of ICI therapy, it is possible to observe a progressive shrinkage of both adrenal glands in follow-up CT scans due to chronic inflammation. However, these changes can be subtle and thus overlooked by radiologists, and there are no widely used standardized criteria to confirm atrophy [34]. In a patient with ICI-induced PAI, we observed shrinkage of both adrenal glands one year after initial diagnosis, which is in concordance with the literature on CT findings for autoimmune PAI (Fig. 1). To the best of our knowledge, to date, no specific radiological patterns of disease have been described in the literature as typical for ICI-induced adrenalitis. Nevertheless, note here that one must recognize that because the majority of these patients have been on replacement steroids, the resultant chronic ACTH suppression may also contribute to adrenal gland shrinkage. It is possible to imagine that developments in the field of

"radiomics," using texture analysis and artificial intelligence algorithms, will help researchers and clinicians to better identify specific imaging patterns of ICI-induced adrenalitis and PAI, even in the early stages of the disease [35].

Treatment of primary adrenal insufficiency

In PAI, replacement therapy, including both glucocorticoids and mineralocorticoids, must be started, although at different doses depending on whether it is a case of chronic asymptomatic PAI or a suspected acute adrenal crisis [23]. The ESMO and ASCO guidelines advise to start 15–30 mg hydrocortisone per day in divided doses in case of asymptomatic AI or mild symptoms (grade 1) and 30–50 mg in case of moderate symptoms (grade 2). In case of more severe presentations (grade 3–4), immediate intravenous or intramuscular administration of 100 mg of hydrocortisone is necessitated. In all cases it is recommended to withhold immunotherapy until the patient is clinically stable. Finally, because ICI-induced PAI causes an irreversible loss of adrenal functions, patients with a confirmed diagnosis of AI are advised to wear a medical alert bracelet and to carry an emergency set with hydrocortisone injection [36,37].

Conclusion

ICI-induced PAI is a rare condition with serious, long-term complications for patients. Timely recognition by clinicians and the start of cortisone suppletion is of vital importance. Diagnosis is based on clinical presentation and biochemical results. Although the role of CT imaging may be limited in the acute setting, specific CT-findings may be related to this irAE. We present a case of bilateral adrenal shrinkage observed by CT imaging in a patient with ICI-induced PAI.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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