CLINICAL VIGNETTE

A Rare Cause of Drug-Induced Adrenal Insufficiency

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Case Presentation

A 67-year-old male with history of metastatic lung adenocarcinoma on pembrolizumab presented to the Emergency Department for evaluation of intractable nausea and vomiting. His symptoms began several weeks prior to presentation several days after receiving his last pembrolizumab infusion. In the days leading up to his ED presentation, he also noted new periumbilical abdominal pain, generalized weakness, and lightheadedness.

On arrival to the Emergency Department, vital signs were remarkable for temperature 96.6°F, HR 76, BP 91/64, SpO2 96% on room air. He was a frail, chronically ill-appearing male. His neck was supple without thyromegaly. His abdomen was flat, nondistended, with no palpable hepatosplenomegaly. His skin was warm, well perfused, with mild hyperpigmentation of the palmar creases. Initial laboratory studies were remarkable for WBC of 10.6K with low grade eosinophilia (12.2%), Na 140, K 4.7, glucose 67. Computed Tomography (CT) of the abdomen and pelvis showed no inflammatory changes, free air, free fluid, or significant lymphadenopathy.

Additional laboratory studies including hepatic panel, lipase, and a morning serum cortisol level were ordered to evaluate the etiology of his intractable nausea and vomiting and intravenous hydration and anti-emetics were initiated. On hospital day #2, laboratory results returned notable for an undetectable 6AM cortisol level (< 0.2 mcg/dL). Based on his clinical presentation and laboratory findings, adrenal insufficiency was felt to be the most likely diagnosis. Endocrinology was consulted and additional hormone levels were drawn including aldosterone, ACTH, and TSH. Corticotropin stimulation test was considered but not pursued as his presentation was compelling for adrenal insufficiency. Stress doses of intravenous hydrocortisone were initiated with rapid resolution of his GI symptoms and improvement in his blood pressures.

Prior to hospital discharge, additional laboratory studies returned notable for an undetectable serum aldosterone level and an undetectable ACTH. His undetectable aldosterone level and cutaneous hyperpigmentation suggested primary adrenal insufficiency, however, his undetectable ACTH raised concern for pituitary insufficiency. Additional pituitary hormone levels returned within the normal range. Further review discovered that his ACTH level was drawn within hours of receiving intravenous hydrocortisone, which likely suppressed endogenous secretion of ACTH. His prevailing diagnosis was deemed to be primary adrenal insufficiency, likely stemming from his immune checkpoint inhibitor therapy. The patient was discharged home on both corticosteroid and mineralocorticoid replacement therapy. Clinically, he has done well; with his latest PET CT showing a complete response to the pembrolizumab without evidence of active or recurrent disease.

Discussion

Immune checkpoint inhibitors (ICI) have transformed the treatment for patients with metastatic lung cancer, renal cell carcinoma, and melanoma. However, immune checkpoint inhibitors can lead to inappropriate activation of the immune system and the development of immune-related adverse events (irAEs). The skin and gastrointestinal tract are most commonly affected, but irAEs may develop in any organ system. Within the endocrine system, case reports of ICI-related thyroid dysfunction, hypophysitis, type 1 diabetes mellitus, and primary adrenal insufficiency have been described[1].

Primary adrenal insufficiency (AI) is a relatively uncommon irAE with an estimated incidence of 0.7%[2]. Many of the reported cases, have been attributed to the administration of nivolumab (44.3%). Other cases have been attributed to ipilimumab (23.6%) or pembrolizumab (11.7%)[1]. The diagnosis of AI is often delayed as many of the presenting signs and symptoms are nonspecific. Fatigue, nausea, vomiting, and anorexia are classic symptoms of AI but can easily be misattributed to a cancer patient's tumor burden or nonspecific adverse reaction to medications. Laboratory findings such as hyponatremia, hyperkalemia, and hypoglycemia may be seen in cases of adrenal crisis but are often absent in more indolent presentations of AI. In patients with secondary AI, electrolyte derangements are even less common and less profound because mineralocorticoid activity is preserved[3].

When AI is suspected, further laboratory investigation with a morning serum cortisol level or corticotropin stimulation test is warranted. A morning cortisol level less than 3 mcg/dL has 100% specificity in ruling in the diagnosis of AI and morning cortisol levels greater than 15 mcg/dL predicts normal response to corticotropin stimulation and excludes the diagnosis of AI. Cortisol levels between 3 and 15 mcg/dL are considered indeterminate and should prompt further investigation with a corticotropin stimulation test. Peak cortisol level < 500 nmol/L

at 30 or 60 minutes after administration is indicative of adrenal insufficiency[4].

Once the diagnosis of AI is established, it is important to distinguish whether the defect is primary, secondary, or tertiary in origin. While glucocorticoid replacement is still the mainstay of treatment, additional hormone(s) may require supplementation depending on the level of the defect. Cutaneous hyperpigmentation is an exam finding specific to primary AI due to increased production of ACTH and α-melanocyte stimulating hormone (α-MSH) in response to decreased cortisol feedback[5]. This hyperpigmentation is present in up to 90% of patients with primary AI and is best appreciated in the palmar creases, over scars, knuckles, and gingival mucosa[6]. However, because it is not a universal finding in primary AI, laboratory evaluation of plasma renin, aldosterone, and morning ACTH levels is also recommended[4]. A high (>4,000 pg/mL) morning ACTH level suggests primary AI, while a low or inappropriately normal ACTH level suggests secondary or tertiary AI. Because aldosterone is secreted by the adrenal cortex, low aldosterone and high plasma renin levels would suggest a diagnosis of primary AI. In contrast, in secondary AI, aldosterone production is unaffected; therefore, both renin and aldosterone levels should be within the normal range[3].

Distinguishing primary from secondary AI is especially important in cases involving immune checkpoint inhibitors. Pituitary insufficiency (i.e. hypophysitis) is one of the most commonly reported endocrine irAEs, with a reported incidence ranging from 6.4% to 13% in large retrospective studies[7, 8, 9]. ICI-associated hypophysitis is characterized by inflammation of the pituitary gland with consequent deficiency in one or more pituitary hormones. Isolated ACTH deficiency and TSH deficiency are more common presentations of ICI-associated hypophysitis[9]. Most of these cases have been reported in the context of either ipilimumab or nivolumab administration[10].

Initial treatment of AI typically involves glucocorticoid replacement with hydrocortisone. When adrenal crisis is suspected, intravenous or intramuscular hydrocortisone should be promptly administered. Stable patients with milder symptoms may be started on oral hydrocortisone at 15-25 mg per day in 2 to 3 divided doses[4]. The primary goal of glucocorticoid replacement is to resolve symptoms related to cortisol deficiency while avoiding symptoms of over-supplementation[3]. Patients with concurrent aldosterone deficiency should receive mineralocorticoid replacement i.e. fludrocortisone, at a starting dose of 50-100 µg per day. Insufficient mineralocorticoid supplementation may result in postural hypotension or syncope, and is a recognized trigger for repeated adrenal crises[3,4].

In contrast to other irAEs caused by immune checkpoint inhibitors, the endocrinopathies are often irreversible and require indefinite hormone replacement[11]. However, immunotherapy may be resumed once hormone replacement has been initiated[12]. Some authors have hypothesized that the development of an irAE may actually be a positive predictor of response to cancer therapy. Several studies have demonstrated a significantly longer progression-free survival in patients who develop irAEs. This effect has been observed among patients with melanoma as well as stage III and IV non-small cell lung cancer treated with immunotherapy[2,12]. However, the mechanisms remain poorly understood and further investigation is needed.

Conclusion

- Diagnosing adrenal insufficiency is often challenging due to its nonspecific signs and symptoms. In cancer patients, symptoms of AI can easily be misattributed to the patient's tumor burden or nonspecific adverse reaction to a medication.
- It is critical to recognize that AI and other endocrinopathies may develop as a result of treatment with immune checkpoint inhibitors. While these endocrinopathies are often irreversible, patients may resume cancer treatment with the immune checkpoint inhibitor once stabilized on hormone replacement.

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