Early onset of nivolumab-induced central adrenal insufficiency in gastric adenocarcinoma

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Abstract

Secondary adrenal insufficiency (AI) due to nivolumab, an immune checkpoint inhibitor, is a common occurrence. The mechanism underlying this phenomenon was believed to be the destruction of endocrine cells triggered by immune activation from the medication. A woman in her 60s developed symptoms of adrenal insufficiency (AI) complicating her sepsis a few days after her first administration of nivolumab for gastric adenocarcinoma treatment. Low morning cortisol, low ACTH and the ACTH stimulation test confirmed the diagnosis of AI. An MRI of the pituitary was normal. It is believed that by the time symptoms develop, a significant portion of the cells may have already been destroyed irreversibly. Life-long hormonal therapy is indicated based on the underlying endocrine disorder. Gastric adenocarcinoma is a serious neoplastic disease. Nivolumab should be continued if necessary for oncologic reasons, with concurrent treatment for adrenal insufficiency as indicated.

Keywords: Nivolumab, Immune checkpoint inhibitor, Central adrenal insufficiency, Secondary adrenal insufficiency, Gastric cancer

Introduction

Immune checkpoint inhibitors have become increasingly used and available for the treatment of various malignancies. Nivolumab, a programmed cell death protein 1 (PD1) inhibitor, received FDA approval for lung cancer and melanoma treatment in 2015, renal cell carcinoma in 2016, and metastatic gastric cancer in 2021.[1] The most common adverse events following treatment with nivolumab include fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea. Immune-related endocrinopathy adverse events, primarily affecting the thyroid followed by the pituitary, have been observed.[1]

Immune-related endocrine events (irEEs) accounts for approximately 8% of immune-related adverse events (irAEs) caused by immune-checkpoint inhibitors (ICIs).[1] ICIs, either anti-CTLA-4 or anti-PD-1, activate T-cells and cell-mediated immune responses against tumor cells.[1–3] Concurrently, they increase tendency towards autoimmunity, resulting in irAEs.[2–4] The risk of developing irEEs appears to be amplified with the combination therapy of anti-CTLA-4 and anti-PD-1 compared to monotherapy.[2]

We report a case of secondary adrenal insufficiency after the administration of nivolumab for the treatment of gastric adenocarcinoma.

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Case Description

A woman in her 60s with a past medical history of gastric adenocarcinoma presented with 1-day of severe lethargy. Three days prior, she had received the first dose of immunotherapy, nivolumab, for adenocarcinoma. She had no previous history of corticosteroid use. She denied fever, respiratory symptoms, chest

pain, or gastrointestinal symptoms, except for chronic cancerous abdominal pain. At an outside facility, she was febrile with a temperature of 38.3°C, and was desaturating with oxygen saturation at 83% on room air, and had hypotension. Computed Tomography scans of the chest with contrast revealed bibasilar consolidation with trace left pleural effusion. The diagnosis of community-acquired pneumonia (CAP) with septic shock was established and treatment included 2 liters of fluid, ceftriaxone, azithromycin, intravenous fluid, and vasopressors. Subsequently, the patient was transferred to our facility for a higher level of care.

On examination, her mean arterial pressure was 61 mmHg while on norepinephrine 2 mcg/min, heart rate was 89 bpm, and oxygen saturation was 99% while on 2 liters of nasal cannula. Dry oral mucosa was noted. The abdominal examination showed mild tenderness without guarding, and lung auscultation revealed bilateral crackles. Other physical examinations yielded unremarkable results

The initial investigation showed no leukocytosis with mild anemia. Sodium levels were borderline low at 135 mmol/L, while potassium levels remained within the normal range at 4.1 mmol/L. Lactate and procalcitonin levels were both within the normal ranges, opposing her clinical presentation of septic shock. Complete blood count and blood chemistry are summarized in Table 1. The respiratory viral panel showed no significant findings. Random cortisol levels upon arrival were low at 22.1 nmol/L. Given these findings, CAP might not have been the only cause of hypotension and lethargy. A low level of random cortisol in the setting of sepsis raised concerns about adrenal insufficiency.

Further investigation was conducted to confirm the diagnosis of adrenal insufficiency. Her morning cortisol level was low at 16.6 nmol/L; the ACTH (cosyntropin) stimulation test, using a dose of 250 mcg of cosyntropin, showed an inadequate response to cortisol level. Her ACTH level was also low at 0.4 pmol/L (normal: 1.59–13.94 pmol/L). ACTH and cortisol levels were measured before initiation of corticosteroid treatment. FSH, LH, prolactin, TSH, and IGF-1 levels were unremarkable (Table 2). Computed Tomography scans of the abdomen and pelvis showed no abnormalities in the adrenal glands. However, concerns were raised

Table 1. Complete Blood Count and Blood Chemistry Results Obtained at Presentation

Investigation	Normal Range	Patient
Complete blood count		
WBC (cells/L)	4.3–11 × 10^3	7.5
Hemoglobin (mmol/L)	7.45–9.93	6.39
Hematocrit (%)	38.0–47.0	31.4
Platelets (cells/L)	150–375 × 10^3	249
Blood chemistry		
Glucose (mmol/L)	136–145	164
BUN (mmol/L)	2.14–7.14	3.93
Creatinine (umol/L)	44.21–106.1	35.37
Sodium (mmol/L)	136–145	135
Potassium (mmol/L)	3.5–5.1	4.1
Chloride (mmol/L)	97–197	95
Bicarbonate (mmol/L)	20–30	24
Lactate (mmol/L)	0.4–2.0	0.7
Procalcitonin (mcg/L)	<0.09	0.05

Table 2. Hormonal Investigations and ACTH Stimulation Test Results

Investigation	Normal Range	Patient
Random cortisol	–	22.1 nmol/L
Morning cortisol	–	16.6 nmol/L
FSH (IU/L)-postmenopause	19.3–100.6	25.5 IU/L
Prolactin (mcg/L)	5.5–26.8	22.7 mcg/L
LH (IU/L)-postmenopause	14.2–52.3	14.4 IU/L
TSH (mIU/mL)	0.27–4.2	4.0
Free T4 (pmol/L)	11.97–21.88	9.5
IGF-1 (nmol/L)	5.36–36.48	12.4
ACTH (pmol/L)	1.59–13.94	0.4
ACTH stimulation test*		
Cortisol baseline (nmol/L)	137.93–579.31	13.8
Cortisol at 30 minutes (nmol/L)	386.21–993.10	157.2
Cortisol at 60 minutes (nmol/L)	386.21–1131.03	223.5

*The reference range is cited from Demers LM: In Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 2006; pp. 2014–2027.

regarding nivolumab-induced hypophysitis potentially leading to secondary adrenal insufficiency. The MRI brain showed no sign of hypophysitis. There were no structural abnormalities of the pituitary gland or infundibulum, and no intra- or suprasellar mass is present. She was diagnosed with secondary adrenal insufficiency, likely resulting from the previous administration of nivolumab.

Intravenous Hydrocortisone 100 mg single dose was administered, followed by 50 mg every 6 hours. She remained afebrile throughout her hospital stay. Norepinephrine was discontinued within 24 hours. Blood cultures and urine cultures yielded negative results. The patient completed a 5-day course of antibiotics for pneumonia.

As her clinical lethargy improved, she was discharged with oral hydrocortisone 15 mg in the morning and 5 mg in the evening. We strongly emphasize to the patient the importance of long-term monitoring and ongoing medical adjustments.

Discussion

Theoretically, ACTH-driven increased production of cortisol during critical illness like septic shock. However, elevated plasma cortisol was always accompanied by low ACTH levels as feedback inhibition. This can be explained by the ACTH-independent, inflammation-driven cortisol production, which can also be from infection resulting in hyperinflammation.[13] Normally, the dose-response of cortisol production in response to ACTH was normal in patients, but patients who have been critically ill for approximately 4 weeks or longer may develop secondary adrenal insufficiency.[5,6] There have been studies that invalidate the use of ACTH stimulation test in critically ill patients and recommended hydrocortisone treatment in suspected patients as the test result can be confounded by the increased cortisol distribution volume in critically ill patients—cortical response <9 μg/dl without indicating adrenocortical dysfunction.[7–9] Therefore, our patient was not chronically critically ill, with a history of previous Nivolumab administration, and the low ACTH with inappropriately low random/morning cortisol levels, regardless of the ACTH stimulation test, raised suspicion of pre-existing HPA axis problem before the admission. The septic shock, a trigger event as a second insult, necessitated her care in the ICU.

Central adrenal insufficiency (AI) due to ICIs has been infrequently reported. There are two distinct forms of irAEs affecting the pituitary glands that can lead to secondary AI: ICI-related isolated adrenocorticotropic hormone deficiency (ICI-IAD) and ICI-related hypophysitis (ICI-H). ICI-IAD is typically the diagnosis of exclusion, believed to arise from the cytotoxic effect of activated T cells stimulated by PD-1 inhibitors, resulting in isolated ACTH deficiency. A case series involving 49 patients with metastatic renal cell carcinoma revealed that 10.2% (5 patients) developed secondary adrenal insufficiency with no signs of hypophysitis on MRI following treatment with nivolumab.[10] Conversely, a cohort study of gastric cancer patients reported an adrenal insufficiency incidence rate of only 1.5% (1 out of 65 patients), indicating its rarity in this context.[11]

The actual mechanism of irEEs is not well understood. One hypothesized mechanism involves the autoimmune-mediated destruction of endocrine cells instigated by ICIs. One proposed mechanism involves the destruction of endocrine cells triggered by immune activation from ICIs.[12] It is believed that by the time symptoms develop, a significant portion of the cells may have already been destroyed or damaged, rendering the damage irreversible.[13] However, there is a potential silver lining to the development of irEEs is that it indicates a clinical response to ICI therapy and correlates with better survival if endocrinopathies are properly managed.[14–15] Most endocrine deficiencies persist permanently, irrespective of the discontinuation of ICI therapy. Most endocrine dysfunctions persist permanently, irrespective of the discontinuation of ICI therapy. Therefore, lifelong hormonal therapy is warranted.[16]

The onset of nivolumab-induced adrenal insufficiency varies, ranging from as early as after the initial infusion administration or even after discontinuation of ICI therapy,[4,17] but typically ranges between 3 to 6 months.[11] In a cohort study, adrenal insufficiency emerged five months following nivolumab therapy, whereas in a case report, it manifested one-year

post-nivolumab therapy.[12,18] Notably, all patients in these case reports demonstrated improvement upon cessation of nivolumab and commencement of a physiological dose of hydrocortisone.[12,18,19] Our patient developed secondary adrenal insufficiency within the initial three days of commencing nivolumab therapy. This underscores the importance of recognizing that adrenal insufficiency can arise at any point subsequent to initiating nivolumab treatment. Nivolumab can block PD-1 for up to 2 months after a single infusion. This explains its anti-tumor effect beyond the treatment duration and may account for the delayed manifestation of irEEs symptoms.[20,21] Monitoring of cortisol or ACTH levels is generally not deemed necessary during monotherapy with anti-PD-1/PD-L1 unless symptoms suggestive of adrenal insufficiency emerge.[1]

In addition to the widely varying severity, symptoms may also be subtle at presentation or confused with inflammatory symptoms of cancer, such as fever, anorexia, and anxiety, making the diagnosis challenging. Given the abrupt onset in this patient, it is crucial to consider and exclude other potential causes, such as septic shock or hypovolemic shock from decreased intake or diarrhea induced by nivolumab. These potential causes warrant empirical treatment until they can be definitively ruled out through appropriate diagnostic evaluation

As irAEs are considered severe adverse events, it is recommended to suspend immunotherapy until symptoms are resolved. Discontinuing anti-PD-1 is typically not necessary if the patients are receiving appropriate hormonal therapy.[1,11] However, gastric adenocarcinoma is a serious neoplastic disease. Nivolumab should be continued if necessary for oncologic reasons, with concurrent treatment for adrenal insufficiency as indicated. According to the European Society of Endocrinology clinical practice guideline, it is recommended that the presence of a controlled endocrinopathy should not prevent the initiation or continuation of ICI therapy. Most patients with confirmed ACTH deficiency are effectively managed with a daily dose of 15–25 mg of hydrocortisone, divided into two or three daily doses. Mineralocorticoids should not be administered in cases of secondary adrenal insufficiency.[22]

Conclusion

Endocrine disorders associated with ICIs often result in permanent hormone deficiencies, necessitating long-term monitoring to prevent serious complications. Patient education is vital in managing adrenal insufficiency, empowering patients to participate actively in their treatment. It is also highly recommended that all patients be closely monitored while on hormonal supplementation and involving an endocrinologist to assist with dose adjustments should be considered. The hormonal therapy with systemic high-dose corticosteroids initially does not differ from AI caused by other etiologies, hydrocortisone, or prednisone. In severe cases, such as adrenal crises or hospitalized situations, patients may require intravenous glucocorticoid and hydration.[1,11,22]

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