SUNTEXT REVIEWS

SunText Review of Case Reports & Images
ISSN: 2766-4589

Open Access
Case Report
Volume 6:1

A Case Report: Immunotherapy-Induced Adrenal Insufficiency

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Received date: 03 February 2025; **Accepted date:** 10 February 2025; **Published date:** 19 February 2025

Citation: Jowfer Deen FEA, Kumar P (2025) A Case Report: Immunotherapy-Induced Adrenal Insufficiency. SunText Rev Case Rep Image 6(1): 150.

DOI: https://doi.org/10.51737/2766-4589.2025.150

Abstract

Immune checkpoint inhibitors (ICIs), such as pembrolizumab, have revolutionized the treatment of various cancers, improving survival rates in multiple malignancies. Despite their clinical efficacy, these therapies are associated with a spectrum of immune-related adverse events (irAEs), including endocrinopathies such as adrenal insufficiency. Although adrenal insufficiency secondary to ICIs is rare, it can be life-threatening if left unrecognized and untreated. This report describes an unusual presentation of pembrolizumab-induced adrenal insufficiency in a 79-year-old female with colorectal cancer. Despite suppressed adrenocorticotropic hormone (ACTH) levels, her serum cortisol remained within the normal range, complicating the diagnosis. The patient's symptoms of nausea, vomiting, and fatigue resolved following corticosteroid therapy, confirming the diagnosis. This case highlights the need for high clinical suspicion of adrenal insufficiency in patients receiving immunotherapy and emphasizes the importance of timely diagnosis and appropriate management to prevent adrenal crisis.

Keywords: Renal cell carcinoma (RCC); Adrenal insufficiency; Endocrinopathies

Introduction

Pembrolizumab is a humanized monoclonal IgG4 antibody that targets the programmed death receptor-1 (PD-1) on T cells, enhancing anti-tumor immunity by preventing T-cell inhibition. This therapy is approved for several malignancies, including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), cervical cancer, and colorectal cancer [1,2]. Although immune checkpoint inhibitors have significantly improved patient outcomes, they are also associated with a variety of immune-related adverse events (irAEs) that can affect multiple organ systems. Among these, endocrine irAEs, such as thyroid dysfunction, hypophysitis, and adrenal insufficiency, are particularly concerning due to their potential for delayed diagnosis and life threatening complications [3,4]. Adrenal insufficiency caused by pembrolizumab is most commonly secondary to autoimmune hypophysitis, in which inflammation of the pituitary disrupts ACTH secretion. This disruption results in secondary adrenal insufficiency, which typically presents with both low ACTH and low cortisol levels. However, the case presented here demonstrates a diagnostic challenge due to the patient's normal cortisol level despite suppressed ACTH, an unusual biochemical profile for this condition.

Case Presentation

A 79-year-old female with a history of colorectal cancer diagnosed in October 2022 presented to the emergency department with a one-week history of intermittent nausea, vomiting, and fatigue. She had undergone a bowel resection in 2022 and had been receiving pembrolizumab every three weeks for the past 18 months. The patient reported large-volume, dark green vomiting (approximately 2 to 4 liters in total) and mild diarrhea, which occurred about two times per day. She denied any associated fever, hematochezia, mucus in the stool, chest pain, palpitations, or dizziness. Her medical history was significant for gastroesophageal reflux disease (GORD), hypertension, and hyperlipidemia.

Emergency department evaluation

Upon presentation, the patient exhibited signs of dehydration, including dry mucous membranes. A physical examination

revealed hepatomegaly, but no other abnormalities were noted. Initial treatment included intravenous (IV) fluids, antiemetics, and proton pump inhibitors (PPIs), but her symptoms showed minimal improvement.

Laboratory and imaging findings

The results of her investigations included a normal computed tomography (CT) scan of the abdomen and pelvis. Blood tests revealed a low urea level of 3.3 mmol/L (reference range 3.5– 9.5 mmol/L) and a markedly suppressed ACTH level of <2 pg/mL (reference range 7–64 pg/mL). Her serum cortisol level was 382 nmol/L, which was within the normal range of 100–535 nmol/L. The white cell count was elevated at 14.9 × 10^9/L (reference range 3.5–10 × 10^9/L), with neutrophilia at 12.38 × 10^9/L (reference range 1.5–6.5 × 10^9/L). Urinalysis showed the presence of leukocytes and erythrocytes above normal levels. Despite her cortisol being within the normal range, the combination of suppressed ACTH and clinical symptoms suggested the diagnosis of secondary adrenal insufficiency [5].

Treatment and Clinical Course

The patient was initially treated with intravenous dexamethasone at a dose of 4 mg three times daily. Her symptoms, including nausea and vomiting, improved significantly, and she was subsequently transitioned to oral hydrocortisone at a dose of 10 mg in the morning and 5 mg in the afternoon. She was discharged home with a steroid tapering plan and scheduled for outpatient follow-up. However, two days after discharge, the patient returned to the emergency department with a recurrence of nausea and vomiting, although the symptoms were less severe than during her initial presentation. An abdominal ultrasound revealed gallbladder wall thickening, multiple gallstones, and a mildly dilated common bile duct measuring 9 mm. No stones were visualized within the duct, and no signs of acute cholecystitis were present. Given her family history of gallstones and her imaging findings, further surveillance was recommended. She was restarted on intravenous dexamethasone, and her symptoms again resolved. The patient was discharged with instructions to continue oral steroids, and follow-up appointments with endocrinology and oncology were arranged.

Discussion

Adrenal insufficiency associated with immune checkpoint inhibitors is a rare but serious condition, most commonly resulting from hypophysitis. Autoimmune inflammation of the pituitary disrupts ACTH secretion, leading to secondary adrenal insufficiency [6]. This condition typically presents with low ACTH and low cortisol levels. However, in this case, cortisol levels remained within the normal range, despite a markedly suppressed ACTH level. This finding complicated the diagnosis and highlights the variability in the biochemical presentation of adrenal insufficiency. Several diagnostic challenges were present in this case. Firstly, the patient's normal cortisol level could have led clinicians to overlook adrenal insufficiency as a potential diagnosis. Secondly, her gastrointestinal symptoms of nausea and vomiting were nonspecific and could have been attributed to other causes, such as gastritis or gallbladder disease. Finally, her symptomatic improvement following corticosteroid therapy provided a crucial diagnostic clue that confirmed the presence of adrenal insufficiency. Failure to recognize adrenal insufficiency in a timely manner can result in adrenal crisis, which is characterized by hypotension, shock, and significant electrolyte disturbances. Early diagnosis and treatment are essential to prevent these life-threatening complications [7]. This case highlights the importance of maintaining a high index of suspicion for adrenal dysfunction in patients undergoing immunotherapy, even when laboratory findings are not entirely consistent with typical presentations.

Conclusion

This case underscores the need for heightened clinical vigilance for adrenal insufficiency in patients receiving immune checkpoint inhibitors. Even when cortisol levels are within the normal range, clinicians should consider the possibility of adrenal insufficiency if ACTH is suppressed and the patient presents with nonspecific symptoms such as nausea, vomiting, and fatigue. A multidisciplinary approach involving oncologists, endocrinologists, and primary care physicians is essential for the timely diagnosis and management of this rare but serious condition. Further research is needed to improve diagnostic accuracy and optimize treatment protocols for immune checkpoint inhibitor-induced endocrinopathies.

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