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Case Report

A Case Report on Nivolumab Induced Hypophysitis

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ABSTRACT

Nivolumab, an immune checkpoint inhibitor, has revolutionized the treatment of various malignancies, including esophageal adenocarcinoma. However, its use is associated with immune-related Adverse Events (irAEs), including hypophysitis, a rare but potentially serious inflammation of the pituitary gland. This case report describes a patient with adenocarcinoma of the lower esophagus who developed hypophysitis after five cycles of nivolumab, presenting with hyponatremia and low cortisol levels. This case highlights the importance of recognizing and managing this endocrine irAE in patients undergoing immunotherapy.

Keywords: Nivolumab, Hypophysitis, Immune Checkpoint Inhibitor, Adverse Events, Esophageal Adenocarcinoma, Immunotherapy.

INTRODUCTION

Adenocarcinoma of the esophagus is a serious esophageal cancer, as late-stage detection frequently results in a poor prognosis (Zhang, 2013). The increasing incidence of esophageal adenocarcinoma has prompted research into various therapeutic modalities, including immunotherapy, surgical resection, and chemotherapy (Rustgi and El-Serag, 2014). The introduction of immune checkpoint inhibitors, such as nivolumab, enhances the immune response against cancer cells by blocking the PD-1 pathway with monoclonal antibodies (Iwama *et al*., 2014).

According to experts, the pathophysiology of Nivolumab-induced hypophysitis is thought to involve an autoimmune mechanism in which the immune system mistakenly attacks the pituitary gland. These immune checkpoint inhibitors are associated with immune-related Adverse Events (irAEs) triggered by immune responses against normal tissues (Postow *et al*., 2018). Recognising and managing such adverse events is critical to ensuring safe immunotherapy treatment.

CASE PRESENTATION

A 75-year-old gentleman patient was admitted to our hospital with endoscopy and biopsy proven adenocarcinoma of the lower esophagus extending to the GE junction. He had presented with dysphagia to solid foods for three months and to liquid for four days, along with significant weight loss. He underwent McKeown's esophagectomy with two-field lymphadenectomy, as part of his treatment protocol.

Following surgery, the patient received five cycles of immunotherapy with Nivolumab. During follow-up, the patient developed drug-induced hypothyroidism, which was confirmed by thyroid function tests (TSH: 15.2 µIU/mL, free T4: 0.7 ng/dL), leading to the initiation of thyroxine therapy.

About one month later, he was readmitted with symptoms of hyponatremia and low cortisol levels, prompting further evaluation for possible nivolumab-induced hypophysitis. Based on the patient's history of Nivolumab treatment, the presence of primary hypothyroidism, and the current laboratory findings (hyponatremia and low cortisol), a diagnosis of nivolumab-induced hypophysitis was made (Table 1). The low cortisol level, in conjunction with a relatively low ACTH level, suggests secondary adrenal insufficiency due to pituitary dysfunction.

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Table 1: Laboratory Profile During Admission for Hypophysitis.

Parameter	Value	Reference Range	Interpretation
Sodium (Na)	125 mmol/L	135-145 mmol/L	Low (Hyponatremia)
Potassium (K)	3.81 mmol/L	3.5-5.1 mmol/L	Normal
Cortisol	12.65 µg/dL	15-25 µg/dL (morning)	Low indicates adrenal insufficiency
TSH	15.2 µIU/mL	0.5-5.0 µIU/mL	Low (Primary Hypothyroidism)
Free T4	0.7 ng/dL	0.8-1.8 ng/dL	Low

DISCUSSION

Nivolumab-induced hypophysitis is an unusual yet clinically significant immune-related side effect that might complicate the management of patients undergoing immunotherapy (Hihara *et al.*, 2019). Although the reported frequency of hypophysitis in patients treated with immune checkpoint inhibitors occurs in only about 0.5% to 1%, early recognition is crucial, as delayed diagnosis can lead to serious complications (Goyal *et al.*, 2021). The clinical presentation of hypophysitis can be insidious; patients often present with fatigue, anorexia, headache, or electrolyte disturbances, which may be misattributed to malignancy progression or chemotherapy side effects (Jessel *et al.*, 2022).

The underlying mechanism of hypophysitis in the context of immune checkpoint inhibitors is not completely understood, but it is believed to involve an autoimmune response triggered by the activation of T-cells against pituitary antigens. This immune-mediated attack can lead to inflammation and dysfunction of the pituitary gland, resulting in hormonal imbalances, including adrenal insufficiency, hypothyroidism, and hypogonadism. In this case, the patient developed symptoms consistent with adrenal insufficiency, which was confirmed by laboratory tests showing low serum cortisol levels (Kotwal, 2021).

Management of nivolumab-induced hypophysitis typically involves the initiation of glucocorticoid therapy to reduce inflammation and restore hormonal balance. The choice of glucocorticoid, dosage, and duration of treatment may vary based on the severity of symptoms and laboratory findings. In this case, the patient was started on a replacement dose glucocorticoid regimen, which led to a significant improvement in symptoms.

The decision to resume nivolumab therapy after the resolution of hypophysitis requires careful consideration of the risks and benefits. While the potential for recurrence of hypophysitis exists, the continuation of effective cancer treatment is crucial for managing the underlying malignancy.

CONCLUSION

This case highlights the importance of patient education regarding the potential side effects of immunotherapy, including the signs and symptoms of hypophysitis. Patients should be informed about the need for regular follow-up and monitoring for endocrine complications, as early recognition and intervention can significantly improve outcomes. Furthermore, this case underscores the need for a multidisciplinary approach in managing patients receiving immunotherapy, involving oncologists, endocrinologists, and other specialists as needed. Prompt diagnosis and appropriate management of endocrine complications are essential to ensure optimal patient care while continuing effective cancer treatment.

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ABBREVIATIONS

irAE: Immune-related Adverse Event; **ACTH:** Adrenocorticotropic Hormone; **GE junction:** Gastroesophageal junction; **TSH:** Thyroid-Stimulating Hormone; **T4:** Thyroxine.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This case report describes a 75-year-old patient with esophageal adenocarcinoma who developed hypophysitis following nivolumab therapy. This report emphasises the importance of early recognition and management of immune-related endocrine complications are critical. A multidisciplinary care approach is necessary to ensure safe in patients undergoing immunotherapy

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