Manejo de la hipofisitis inducida por ipilimumab en el carcinoma hepatocelular avanzado: Una perspectiva clínica

Navigating Ipilimumab-induced hypophysitis in advanced hepatocellular carcinoma: A clinical perspective

Luis Carlos Afonso Rocha[1], Cecilia Moreira[2], Filipe Breda[1], José Presa[3]

[1] Centro Hospitalar Vila Nova de Gaia/Espinho (Portugal)
[2] Unidade Local de Saúde de Matosinhos (Portugal)
[3] Centro Hospitalar de Trás-os-Montes e Alto Douro (Portugal)

ABSTRACT

Immunotherapy, represented by immune checkpoint inhibitors (ICIs), has marked a significant breakthrough in cancer treatment. Ipilimumab (IPI), an anti-CTLA-4 agent, stands out in this therapeutic landscape. However, its efficacy is not without challenges, among them, immune-related adverse events, especially hypophysitis.

In this article, we present a detailed clinical case of hypophysitis induced by the combined administration of Ipilimumab (IPI) and Nivolumab (NIVO) in a 69-year-old patient diagnosed with advanced hepatocellular carcinoma (HCC). The complexity of his medical history adds layers of intricacy to the clinical narrative. After four cycles of immunotherapy, a spectrum of symptoms emerged, requiring a multidisciplinary diagnostic and therapeutic approach.

The case highlights the imperative need to understand in nuanced detail ICI-induced hypophysitis. The discussion encompasses the elusive pathophysiology, diverse clinical manifestations, and the delicate balance required for effective clinical management. Significantly, the decision-making regarding treatment continuation is explored, emphasizing the critical need for specialized clinical vigilance.

This case serves as a microcosm of the broader challenges entrenched in the dynamic realm of immunotherapy. As ICIs redefine treatment paradigms for HCC, awareness of rare complications such as hypophysitis becomes indispensable. The conclusion advocates for a multidisciplinary approach to navigate these intricacies, ensuring judicious decision-making and optimal patient outcomes.

Keywords: Immunotherapy, hepatocellular carcinoma, Ipilimumab, hypophysitis, multidisciplinary approach.

RESUMEN

La inmunoterapia, representada por los inhibidores de los puntos de control inmunitarios (ICI), ha supuesto un avance significativo en el tratamiento del cáncer. El ipilimumab (IPI), un agente anti-CTLA-4, destaca en este panorama terapéutico. Sin embargo, su eficacia no está exenta de desafíos, entre ellos, los acontecimientos adversos relacionados con el sistema inmunitario, especialmente la hipofisitis.

En este artículo presentamos un caso clínico detallado de hipofisitis inducida por la administración combinada de ipilimumab (IPI) y nivolumab (NIVO) en un paciente de 69 años diagnosticado de carcinoma hepatocelular (CHC) avanzado. La complejidad de su historia clínica añade capas de complejidad al relato clínico. Tras cuatro ciclos de inmunoterapia, apareció un espectro de síntomas que requirió un enfoque diagnóstico y terapéutico multidisciplinar.

El caso pone de relieve la necesidad imperiosa de comprender en detalle los matices de la hipofisitis inducida por ICI. La discusión abarca la elusiva fisiopatología, las diversas manifestaciones clínicas y el delicado equilibrio necesario para un tratamiento clínico eficaz. De manera significativa, se explora la toma de decisiones respecto a la continuación del tratamiento, enfatizando la necesidad crítica de una vigilancia clínica especializada.

Este caso sirve de microcosmos de los retos más amplios que se plantean en el dinámico ámbito de la inmunoterapia. A medida que las ICI redefinen los paradigmas de tratamiento del CHC, se hace indispensable conocer complicaciones poco frecuentes como la hipofisitis. La conclusión aboga por un enfoque multidisciplinar para navegar por estos entresijos, garantizando una toma de decisiones juiciosa y unos resultados óptimos para los pacientes.

Palabras clave: Inmunoterapia, carcinoma hepatocelular, Ipilimumab, hipofisitis, enfoque multidisciplinar.

INTRODUCTION

Immunotherapy, utilizing immune checkpoint inhibitors (ICI), signifies a noteworthy advancement in cancer treatment. To date, regulatory agencies such as the FDA (Food and Drug Administration) and the EMA (European Medicines Agency) have approved three classes of ICI: anti-CTLA-4 (Citotoxic T-Lymphocyte Antigen 4), anti-PD-1 (Programmed Cell Death Protein 1), Anti-PD-L1 (Programmed Death-Ligand 1).[1]

Ipilimumab (IPI), by blocking CTLA-4, restores the activation and proliferation of T lymphocytes, enhancing the anti-tumor response. FDA-approved in 2011 for the treatment of metastatic or unresectable melanoma, IPI has shown effectiveness not only in this type of cancer but also in other neoplasms such as lung carcinoma, renal cell carcinoma, and advanced hepatocellular carcinoma (HCC)[2]. Nivolumab (Nivo) is an anti-PD-1 drug approved in 2014.[3]

The use of IPI, like other ICI, is associated with immune-related adverse events affecting the skin, gastrointestinal tract, liver, and endocrine system[4]. Hypophysitis, a rare and potentially serious complication, surfaces within this spectrum.

Correspondencia: 12475@ulsge.min-saude.pt
Cómo citar este artículo: Afonso LC, Moreira C, Breda F, Presa J.
Navigating Ipilimumab-induced hypophysitis in advanced hepatocellular carcinoma: A clinical perspective. Galicia Clin 2024; 85-4: 34-36.
Recibido: 27/11/2023 ; Aceptado: 24/02/2024 // https://doi.org/10.22546/75/4212

Hypophysitis represents a heterogeneous group of inflammatory lesions affecting the pituitary gland. The pathophysiology involves immune dysregulation and inflammation, though the exact mechanisms are not fully understood. It is categorized based on histology and/or primary or secondary etiology, which may be related to systemic diseases, infections, or pharmacological agents[5]. It is a relatively rare disease with an annual incidence of 1/9,000,000.[6]

The incidence of hypophysitis in patients treated with IPI varies from 1.8% to 17%, depending on the doses and treatment regimens used. Although IPI has demonstrated significant clinical benefits, it has also been associated with a higher incidence of hypophysitis compared to other ICI.[5]

Our aim is to provide a comprehensive understanding of ICI-induced hypophysitis and raise awareness about this complication.

CLINICAL CASE

We present the case of a 69-year-old man with a medical history encompassing dyslipidemia, type 2 diabetes *mellitus*, hypertension, hypothyroidism, benign prostatic hyperplasia, atrial fibrillation, and chronic liver disease of viral and alcoholic etiology, complicated by a large HCC. The patient had previously undergone transarterial chemoembolization (TACE) and first-line treatment with Sorafenib, which was discontinued due to cardiovascular dysfunction and gastrointestinal symptoms. Subsequently, he initiated second-line systemic treatment with IPI and Nivo. The treatment regimen comprised 4 cycles of immunotherapy, with Nivo at 1 mg/kg plus IPI at 3 mg/kg, administered every 3 weeks (4 doses), followed by Nivo at 240 mg every 2 weeks.

Following the completion of the initial 4 cycles, the patient presented to the Liver Unit with complaints of anorexia, asthenia, dizziness, and headaches, evolving over two weeks.

Laboratory analysis revealed hyponatremia (127 mmol/L) and evidence of adrenal insufficiency, manifested by low levels of adrenocorticotropic hormone (ACTH) (1.5 pg/mL) and cortisol (21 nmol/L). Additionally, there was a decrease in insulin-like growth factor (IGF-1) levels (22.6 ng/mL), with no changes in anti-thyroid antibodies, thyroid function hormones, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Prompt diagnosis of secondary hypophysitis due to IPI + Nivo treatment was established.

The patient was admitted to the Internal Medicine ward and initiated treatment with hydrocortisone at 50 mg every 8 hours. Cranioencephalic magnetic resonance imaging (MRI) revealed no abnormalities in pituitary morphology. Abdominal computed tomography (CT) scan indicated a partial therapeutic response, with a reduction in the size of the hepatic neoplastic lesion (from 6.7 cm to 4.7 cm), without other associated complications. Following one week of hospitalization, the patient was discharged with normalized laboratory values. Levothyroxine was adjusted to 50 mcg/day, while hydrocortisone was maintained at a dose of 15 mg + 10 mg. The patient was referred for an endocrinology consultation. Upon reevaluation by the multidisciplinary board, the decision to discontinue immunotherapy was made due to the severity of adverse events after completing four therapy cycles. A comprehensive assessment by the hepatobiliary surgery team recommended surgical removal of the HCC, which proceeded without documented complications.

DISCUSSION

Recent clinical trials unequivocally highlight the potential of IPI, both as monotherapy and in combination with other modalities, to generate a strong antitumor response and improve overall survival in advanced HCC patients.

Understanding the pathophysiology of ICI-induced hypophysitis is crucial for precise diagnosis and effective clinical management. Although the exact mechanisms are not fully understood, a consensus suggests immune dysregulation leading to pituitary gland inflammation. Hypotheses include autoimmune-mediated damage to pituitary cells, direct T lymphocyte infiltration, and the release of pro-inflammatory cytokines.[5]

Contrary to other endocrinopathies, hypophysitis typically does not necessitate suspension of ICI therapy, as it does not significantly impact the likelihood of pituitary function recovery[2]. However, the nonspecific nature of symptoms implies that many cases may go unrecognized without a high degree of clinical suspicion. Regular evaluation of thyroid function tests before each treatment cycle is recommended. A decline in Thyroid Stimulating Hormone (TSH) has shown potential as a predictive factor for IPI-induced hypophysitis[7], with a ≥ 80% decrease in TSH serving as an early predictor[6]. Treatment primarily involves hormonal replacement of the affected pituitary axes with hydrocortisone and levothyroxine.

The ideal glucocorticoid (GC) dose to alleviate hypophysitis-related symptoms is uncertain. Recent studies indicate no clear benefit in pituitary function recovery or mortality with high-dose GC; in fact, it's linked to increased mortality. Current guidelines recommend high-dose GC solely for symptomatic patients. While pituitary inflammation often resolves within three months, resulting adrenal insufficiency may persist long-term, irrespective of the GC dose administered.[8]

Understanding and managing adverse events is vital for maximizing the benefits of Immune ICI treatment while minimizing risks. This case underscores the ongoing challenges in immunotherapy. ICI's transformation of HCC treatment emphasizes the need for a comprehensive understanding, early detection, and specialized intervention for rare complications like hypophysitis. While not mandating treatment suspension, specialized vigilance is crucial, emphasizing a multidisciplinary approach in evaluation and decision-making.

As cancer treatment evolves with immunotherapy, continual vigilance and a multidisciplinary approach are essential. This case stresses the importance of ongoing research, education, and clinical collaboration to optimize ICI benefits in HCC while navigating potential complications. The pursuit of precision and personalized care remains critical for enhancing patient outcomes in the dynamic realm of cancer immunotherapy.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interests.

SOURCE OF FUNDING
This research had no funding sources.

ETHICAL ASPECTS
All participants submitted a consent form to be included in this study.

BIBLIOGRAPHY

1. Tan MH, Iyengar R, Mizokami-Stout K, Yentz S, MacEachern MP, Shen LY, et al. Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients: a scoping review of case reports. Clin Diabetes Endocrinol. 2019;5:1.
2. Joshi MN, Whitelaw BC, Palomar MT, Wu Y, Carroll PV. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review. Clin Endocrinol (Oxf). 2016;85(3):331-9.
3. Faje A, Reynolds K, Zubiri L, Lawrence D, Cohen JV, Sullivan RJ, et al. Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis. Eur J Endocrinol. 2019;181(3):211-219.
4. Cukier P, Santini FC, Scaranti M, Hoff AO. Endocrine side effects of cancer immunotherapy. Endocr Relat Cancer. 2017;24(12):T331-T347.
5. Tsoli M, Kaltsas G, Angelousi A, Alexandraki K, Randeva H, Kassi E. Managing Ipilimumab-Induced Hypophysitis: Challenges and Current Therapeutic Strategies. Cancer Manag Res. 2020;12:9551-9561.
6. Siddiqui MS, Lai ZM, Spain L, Greener V, Turajlic S, Larkin J, et al. Predicting development of ipilimumab-induced hypophysitis: utility of T4 and TSH index but not TSH. J Endocrinol Invest. 2020;44(1):195-203.
7. Faje AT, et al. Ipilimumab-Induced Hypophysitis: A Detailed Longitudinal Analysis in a Large Cohort of Patients with Metastatic Melanoma. J Clin Endocrinol Metab. 2014;99(11):4078-4085.
8. Snyders T, Chakos D, Swami U, Latour E, Chen Y, Fleseriu M, et al. Ipilimumab-induced hypophysitis, a single academic center experience. Pituitary. 2019;22(5):488-496.