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Five-Year Sustained Response to Nivolumab in Hepatocellular Carcinoma following Serious Immune-Related Hepatitis

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Keywords
Hepatocellular carcinoma · Immune checkpoint inhibitors · Nivolumab · Drug-related side effects and adverse reactions · Progression-free survival

Abstract
Introduction: Hepatocellular carcinoma (HCC) holds high cancer mortality worldwide. Immunotherapy-based combination therapy, currently the first-line (1L) standard of care in advanced HCC, has shifted the treatment paradigm concerning both efficacy and safety outcomes. Data on immune-related adverse event surrogacy for efficacy outcomes are mixed. ***Case Report:*** We report the case of a 58-year-old male with chronic hepatitis C virus infection who presented with a voluminous shoulder HCC metastasis. Albeit an initial significant biochemical response with 1L sorafenib, progressive disease after 3 months plus a bleeding complication led to treatment discontinuation. Second-line nivolumab, although yielding a rapid clinical and biochemical response, was permanently ceased after 12 weeks due to a grade 3 immune-related hepatitis. Notably, 5 years post-treatment, the patient sustains a major biochemical and radiographic response. ***Discussion:*** This case highlights an unusual and sustained response to nivolumab treatment in HCC, following early treatment discontinuation due to severe hepatotoxicity.

Resposta mantida a nivolumab por cinco anos no carcinoma hepatocelular após hepatite imunomediada grave

Palavras Chave
Carcinoma hepatocelular · Inibidores de checkpoint imunitário · Nivolumab · Reações adversas e efeitos colaterais associados a medicamentos · Sobrevivência livre de progressão

Resumo
Introdução: O carcinoma hepatocelular (CHC) contribui significativamente para a mortalidade por cancro a nível mundial. As terapêuticas de combinação com imunoterapia, atualmente primeira-linha (1L) terapêutica no CHC avançado, alteraram o paradigma terapêutico em termos de eficácia e segurança. Não é claro, à luz da

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evidência atual, que exista uma associação entre efeitos adversos imunomediados e eficácia da imunoterapia. ***Caso Clínico:*** Reportamos o caso de um homem com 58 anos e antecedentes de infeção crónica por vírus de hepatite C que se apresentou com uma volumosa metástase de CHC no ombro. Apesar da expressiva resposta bioquímica conferida, o sorafenib em 1L foi interrompido aos 3 meses mediante progressão de doença e toxicidade hemorrágica. A segunda-linha terapêutica com nivolumab conferiu uma rápida resposta clínica e bioquímica, no entanto foi suspensa após 12 semanas devido a uma hepatite imunomediada grau 3. Ressalva-se, 5 anos após a interrupção de nivolumab, manutenção de resposta bioquímica e imagiológica. ***Discussão:*** O caso apresentado destaca uma resposta rara e mantida a nivolumab num doente com CHC após descontinuação precoce da terapêutica por hepatotoxicidade severa.

Introduction

Accounting for 7.8% of cancer deaths, liver cancer is the third leading cause of cancer mortality worldwide [1]. Hepatocellular carcinoma (HCC), which comprises nearly 90% of liver cancers, has moved from low to high socio-demographic index regions. Nevertheless, viral hepatitis remain predominant risk factors: in the Western world, chronic hepatitis C virus (HCV) is the most common HCC aetiology, while only 20% of HCC cases are attributed to hepatitis B virus [2]. Regarding viral hepatitis, the strongest predictors for HCC are the presence of underlying cirrhosis and unattaining sustained virological response (SVR), although the risk is not negligible even after SVR [3]. Unfortunately, whether due to late-stage diagnosis or local treatment failure, most HCC patients require systemic therapy [4].

In 2024, immunotherapy (IO) is paramount to advanced HCC (aHCC) treatment. First-line (1L) IO-based combination therapy is currently standard of care for all fit patients without contraindications [5, 6]. Recent trials also brought innovation concerning aHCC monotherapy: following a series of negative trials, the phase III HIMALAYA trial showed a statistically significant non-inferiority of durvalumab versus sorafenib [7]. Nivolumab, an anti-programmed cell death-1 (PD-1) monoclonal antibody (mAb), was one of the first immune checkpoint inhibitors (ICIs) deemed active against HCC. Based on the CheckMate-040 trial, in September 2017, the Food and Drug Administration (FDA) granted nivolumab accelerated approval for patients with aHCC previously treated with sorafenib [8, 9]. In 2018, the European Society for Medical Oncology (ESMO) guidelines featured nivolumab as an alternative for aHCC patients unfit for TKI (evidence level III, recommendation grade C) [10].

With the extensive use of ICIs, the prevalence of immune-related adverse events (IRAEs) has risen. While studies proposing IRAEs as surrogate markers for survival outcomes have accumulated, recent data on this topic are mixed [11, 12]. Moreover, long-term survival benefits, often captured in early plateau survival curves among IO-treated populations, are less clear in HCC trials [7, 13, 14]. We report the case of a 58-year-old male with an atypical aHCC presentation, who currently sustains response to second-line (2L) nivolumab 5 years after early discontinuation due to a severe immune-related (IR) hepatitis.

Case Report

A 58-year-old male presented at our institution in November 2018 with a progressively growing mass and worsening pain in his left shoulder, first noticed in August 2018. He had a past medical history of HCV genotype 3a infection without SVR at 6 weeks post-12-week sofosbuvir/daclatasvir treatment in November 2017, following which he was lost to follow-up in the hepatology outpatient clinic. He was also a former smoker (30 pack-years), with unquantified alcohol and heroin consumption, both ceased 20 years prior.

Following a tendinitis presumption and unsuccessful physiotherapy, a shoulder CT scan showed a left scapular lytic lesion infiltrating the surrounding supraspinatus, subscapular, infraspinatus, and deltoid muscles, measuring 137 mm in long axis. Comprehensive evaluation for tumour markers showed a markedly elevated alfa-fetoprotein (AFP) (>80,000 ng/mL; normal range [NR] <8.78 ng/mL). Contrast-enhanced body CT scan documented two liver nodules in segments V and VI without venous washout, respectively, measuring 30 mm and 20 mm, without additional remarkable findings. Bone scintigraphy was negative for additional sites of bone involvement. Our tumour board advocated a shoulder tumour biopsy, which revealed a poorly differentiated carcinoma, negative for both cytokeratin 7 and 20, weakly positive for cluster of differentiation 99 (CD99) and positive for AE1/AE3, CAM 5.2, and hepatocyte antigen. Given absent unequivocal imaging

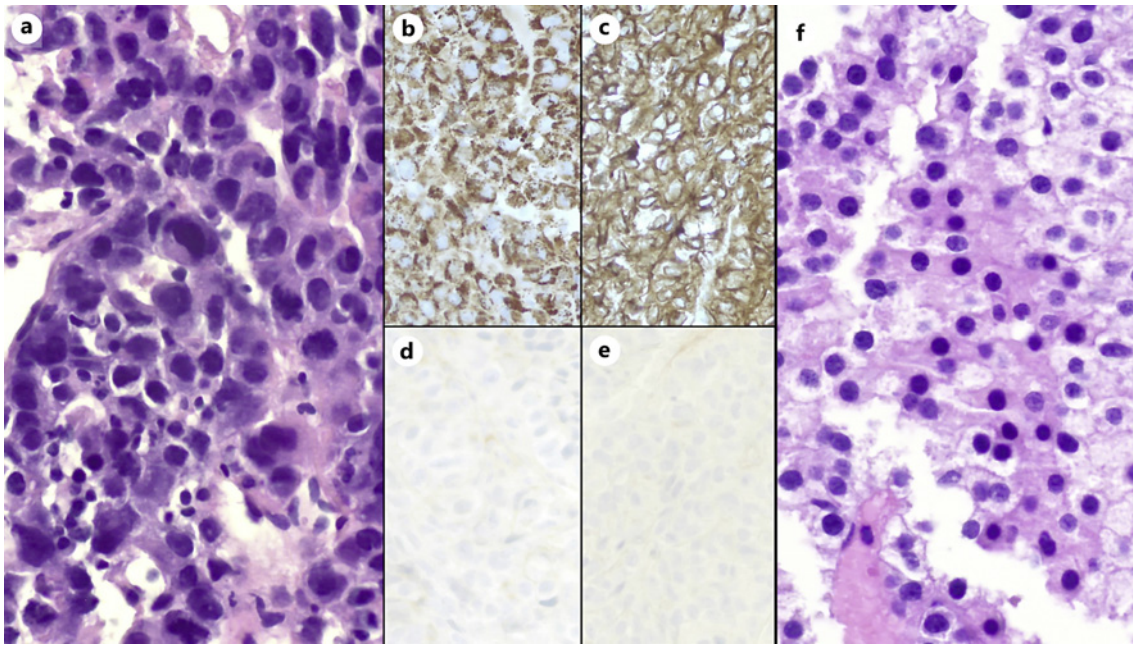

Fig. 1. a Haematoxylin and eosin stain (H&E) magnification ×400; Shoulder mass biopsy revealed a proliferation of highly atypical epithelioid cells with multiple mitotic figures and apoptotic bodies. The cells were positive for HepPar1, cytokeratins AE1/AE2 and negative for cytokeratins 7 and CK20, consistent with a carcinoma of hepatic origin. **b** H&E magnification at ×200. Shoulder mass biopsy. The cells were positive for HepPar1. **c** H&E magnification at ×200. Shoulder mass biopsy. The cells were positive for cytokeratins AE1/AE2. **d** H&E magnification at ×200. Shoulder mass biopsy. The cells were negative for CK7. **e** H&E magnification at ×200. Shoulder mass biopsy. The cells were negative for CK20. **f** H&E magnification ×400; Liver biopsy showed a mostly solid proliferation of polygonal epithelioid cells with clear eosinophilic cytoplasm, consistent with HCC (Grade II).

features allowing HCC identification, subsequently performed liver biopsy confirmed an Edmonson-Steiner grade 2 HCC in a non-cirrhotic liver (moderate mononucleated portal infiltrate; macrovesicular steatosis; Ishak fibrosis score 1) (shown in Fig. 1).

In February 2019, the patient was admitted to our Medical Oncology Department. He remained overweight, despite a 5 kg loss since first noting the scapular mass (height 175 cm; weight 80 kg; body mass index 26.12 kg/m^2). Before starting systemic treatment, the patient underwent three-dimensional conformal radiotherapy to his left shoulder between 14 and 26 February 2019 (30 Gy, 3 Gy/day in 10 fractions), achieving successful pain management. Classified as Barcelona Clinic Liver Cancer (BCLC) stage C (extrahepatic spread with preserved liver function and performance status), ECOG performance status 1, and Child-Pugh score A5, our patient started 1L sorafenib 400 mg twice daily. Treatment baseline images of the scapular tumour are shown in Figure 2. Despite achieving a significant biochemical response (AFP nadir was 17,349 ng/mL at the end of April 2019; NR <8.78 ng/mL), a short time to progression was observed: 3 months into sorafenib, follow-up body CT scan revealed shoulder metastasis progression (201.1 mm long axis, +47%) and a new-onset right adrenal gland haematoma resulting from a new haemorrhagic metastasis (117 mm long axis). Given the class-related haemorrhagic complication upon rapid progression on sorafenib, he was thus proposed to 2L IO: off-label nivolumab 240 mg every 2 weeks was started in July 2019 (baseline AFP of 77,687 ng/mL; NR <8.78 ng/mL). Two cycles into therapy, no relevant safety signals were reported, while AFP had decreased significantly to 1,890 ng/mL (NR <8.78 ng/mL).

Conversely, after completing 6 nivolumab cycles, in September 2019, although asymptomatic, the patient's blood tests showed new-onset elevated alanine aminotransferase (ALT) of 203 U/L (NR <55 U/L), aspartate aminotransferase (AST) of 301 U/L (NR 5–34 U/L), gamma-glutamyl transferase of 206 U/L (NR 12–64 U/L), and alkaline phosphatase of 160 U/L (NR 40–150 U/L); total bilirubin (0.74 mg/dL; NR 0.2–1.2), albumin (40.1 g/L; NR 35–52), international normalized ratio (1.08; NR 0.8–1.2), activated partial thromboplastin time (34.7 s; NR 25.1–36.5) were normal, while AFP kept declining (127.8 ng/mL; NR <8.78 ng/mL). Viral hepatitis, vascular aetiology, and new hepatotoxic medication were

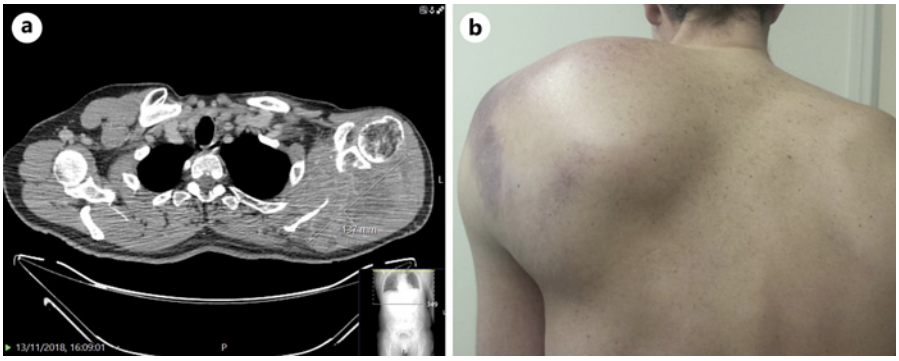

Fig. 2. a Left scapular metastasis measuring 137 mm in long axis shown in the sorafenib baseline CT scan (November 2018). **b** Patient's left shoulder tumour before starting first-line sorafenib in February 2019.

excluded. In fact, HCV viral load had decreased from 7.57 log in November 2017 to 6.48 log in September 2019. Ultimately, a grade 3 (Common Terminology Criteria for Adverse Events, version 5.0) nivolumab-induced hepatitis was assumed. Oral prednisolone was started at 1 mg/kg/day (80 mg daily), and nivolumab was suspended. Blood tests were repeated every 3 days over the following 3 weeks. In October 2019, ALT had declined to normality (48 U/L; NR <55 U/L), while AST neared the NR (38 U/L; NR 5–34 U/L). In November 2019, after completing steroid weaning, a rebound elevation of liver tests (AST 150 U/L [NR 5–34], ALT 80 U/L [NR <55], gamma-glutamyl transferase 114 U/L [NR 12–64], alkaline phosphatase 129 U/L [NR 40–150]) led to prednisolone resumption at 20 mg/day. In January 2020, a definitive wean had been successfully carried out and liver parameters were within NR. In March 2020, body CT scan demonstrated a meaningful partial response, with complete liver nodule remission, as well as reduction of both adrenal (117 to 40 mm long axis, −66%) and scapular lesions (201 to 147 mm, −37%). Nivolumab was not resumed given our patients' radiological response, AFP kinetics (14.78 ng/mL in January 2020; NR <8.78 ng/mL), and risk of iatrogenesis upon rechallenge. AFP, ALT, and AST kinetics are shown in Figure 3.

Our patient has remained on active surveillance. Follow-up in the hepatology outpatient clinic resumed in September 2021. Repeated HCV genotyping revealed genotype 3a. At that point, the patient was reluctant to retreatment; hence, surveillance including periodic elastography imaging was kept. In September 2024, amid worsened liver fibrosis (10.4 kPa), the patient is awaiting approval for retreatment with sofosbuvir and glecaprevir/pibrentasvir. Regarding HCC surveillance, periodical CT scans revealed further reductions of both adrenal (18 mm, −85%) and scapular (99 mm, −49%) lesions (shown in Fig. 4, 5). AFP levels also kept decreasing and remained within NR (3.48 ng/mL in July 2024; NR <8.78 ng/mL). Six years after the aHCC diagnosis and 5 after ceasing nivolumab, our patient remains alive with responsive disease and fully asymptomatic.

Discussion

HCC bone involvement accounts for grossly 25% of HCC extrahepatic spread. Often consisting of hypervascular soft tissue tumours with concurrent cortex destruction, typical axial skeleton tropism contrasts with the single, bulky shoulder lesion herein reported, initially suggestive of sarcoma, albeit later excluded through immunohistochemistry [15]. Moreover, HCV-related HCC incidence in non-cirrhotic livers ranges from 4.4% to 10.6%. Besides the direct oncogenic HCV effect towards several gene products, previous alcohol abuse may synergistically contribute to the genotoxic effect [16]. Although metabolic dysfunction-associated liver disease could be argued to play a role concerning HCC development in an overweight, non-cirrhotic patient, absent metabolic syndrome criteria in our patient do not favour this proposition. Noteworthy, macrovesicular steatosis and portal inflammation are well described in alcohol-induced liver injury [17]. Our patient did not achieve SVR post-12-week sofosbuvir/daclatasvir treatment. Retrospective data suggest earlier stage HCC could benefit from direct-acting antivirals, given it lessens HCV-related liver impairment precluding optimal HCC local therapy/downstaging. Conversely, data on aHCC BCLC B-C patients benefiting from direct-acting antivirals are lacking [18].

Our patient received 1L sorafenib, standard treatment in aHCC up to 2019. Published in 2018, data from the REFLECT trial offered a case for lenvatinib, particularly given a significant objective response rate (odds ratio 5.01, 95% confidence interval [CI] 3.59–7.01, $p < 0.00001$) and progression-free survival (hazard ratio [HR] 0.64,

Fig. 3. a Alpha-fetoprotein kinetics. First-line sorafenib was started on the 29th February 2019 and stopped on the 21st of May 2019. Nivolumab was started on the 1st July 2019 and 6 cycles were completed on the 23rd September 2019. **b** Alanine aminotransferase and aspartate aminotransferase kinetics. Prednisolone 80 mg daily was started on the 25th of September 2019 and tapered until the 31st of October 2019. Resumption at 20 mg daily was started on the 27th of November 2019 and tapered off again until the 8th January 2020.

95% CI: 0.55–0.75, $p < 0.0001$) [19]. At the time, lenvatinib was not available in our department. Regorafenib, cabozantinib, and ramucirumab remain standard sequence treatment to aHCC who have tolerated sorafenib but progressed (evidence level I, recommendation grade A) [10]. However, further TKIs were unsuitable following class-related toxicity upon progression, hence prompting 2L IO.

At the time, data from the phase I/II CheckMate-040 trial reporting a median overall survival (mOS) of 15.6 months (95% CI: 13.2–18.9) in the expansion cohort progressing on sorafenib had led to nivolumab recommendation in this setting [8, 10]. In 2020, the phase III IMbrave150 trial-positive outcomes for atezolizumab plus bevacizumab versus sorafenib in untreated aHCC patients (mOS 19.2 vs. 13.4 months, HR 0.66, 95% CI:

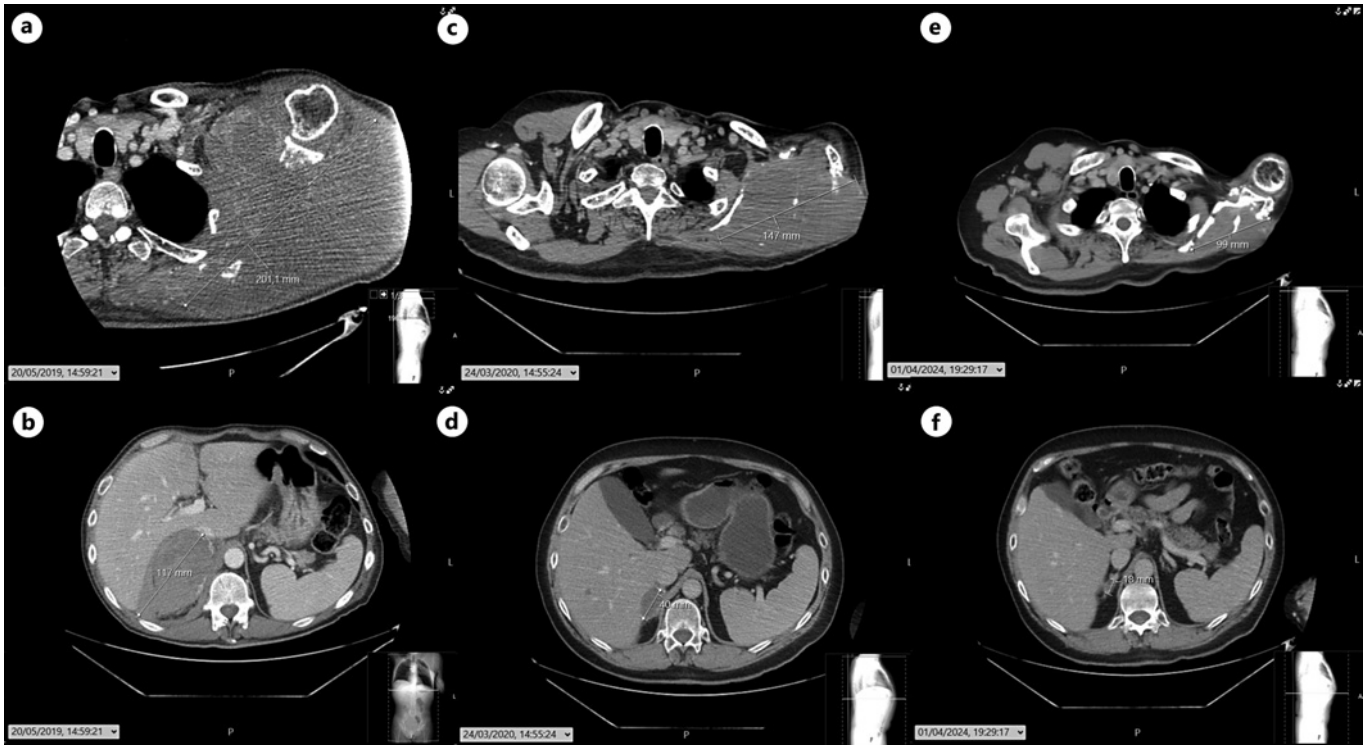

Fig. 4. a Left scapular metastasis measuring 201 mm in long axis shown in nivolumab baseline CT scan (May 2019). **b** New-onset bleeding in the right adrenal metastasis measuring 117 mm in long axis shown in the nivolumab baseline CT scan (May 2019). **c** Left scapular metastasis measuring 147 mm in the long axis corresponding to first nivolumab radiographical response assessment, –37% in size (March 2020). **d** Right adrenal nodule measuring 40 mm in long axis corresponding to first nivolumab radiographical response assessment, –66% in size (March 2020). **e** Left scapular metastasis measuring 99 mm in long axis, –49% in size (April 2024). **f** Right adrenal nodule measuring 18 mm in long axis, –85% in size (April 2024).

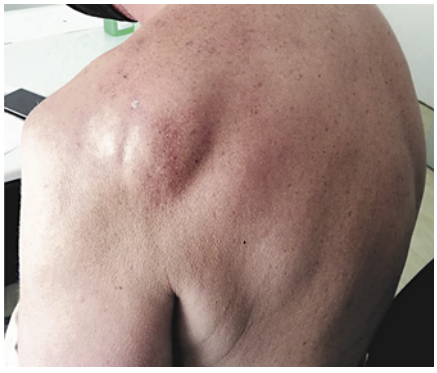

Fig. 5. Responsive left shoulder tumour was documented 2 years after discontinuing nivolumab (September 2021).

0.52–0.85, $p = 0.0009$) defined the combination treatment as new 1L standard of care in the updated ESMO treatment recommendations for HCC [13]. Notwithstanding, in 2021, the confirmatory CheckMate-459 trial comparing 1L nivolumab versus sorafenib did not show a benefit of nivolumab over sorafenib (mOS 16.4 vs. 14.7 months, HR 0.85, 95% CI: 0.72–1.02, $p = 0.07$), leading to the former approval being withdrawn [20]. Likewise, a series of succeeding phase clinical trials failed to show a survival benefit of IO over single-agent TKI [14]. Recently, HIMALAYA trial showed single-dose tremelimumab regular interval durvalumab regimen superiority compared to sorafenib. Furthermore, this trial also established durvalumab monotherapy as the first ICI unbeaten by sorafenib [7, 14]. Notably, data from the CheckMate 9DW trial presented during the 2024 American Society of Clinical Oncology Annual Meeting showed 1L ipilimumab plus nivolumab OS benefit versus sorafenib or lenvatinib (mOS 23.7 vs. 20.6 months, HR 0.79, 95% CI: 0.65–0.96, $p = 0.018$) [21].

The reported deep, durable response to nivolumab in our patient suggests a subset of patients for whom IO may be particularly effective. CheckMate-459 trial exploratory subgroup analysis proposes an OS benefit for patients

overexpressing AFP (≥400 μg/L, HR 0.67, 95% CI: 0.51–0.88), contrary to tumour cell PD-L1 expression (1% cutoff, immunohistochemistry staining using clone 28-8) [20]. To date, conventional IO-predictive biomarkers remain unreliable in HCC [22].

Lastly, this case feeds into IRAEs' surrogacy for survival outcomes. During ICI monotherapy, IR hepatitis incidence ranges between 5 and 10% (1–2% grade 3), although higher incidences are reported among patients with primary liver cancer [23]. Excluding differential diagnoses is mandatory, albeit liver biopsy is often unwarranted. According to the ESMO guidelines published in 2022, grade 3–4 IR hepatitis prompts ICI interruption and initiation of steroids at 1–2 mg/kg/day of (methyl) prednisolone. Of note, retreatment can be equated after such events on a case-by-case basis [23]. Although concomitant liver disfunction did not occur, continuously decreasing AFP seen after ICI interruption, meaningful radiological response and risk of severe iatrogenesis upon rechallenge led to the decision of not resuming ICI in the case presented herein. Also, the occurred rebound elevation of liver tests prompted a more conservative approach. A prospective study including 23 patients with ICI retreatment after severe IR hepatitis found an IR hepatitis recurrence rate of 34.8%. Of note, all recurrences were severe (i.e., grade 3–4) [24]. Also, a large pharmacovigilance cohort study reported a 28.8% IRAE recurrence rate after ICI retreatment, with higher recurrence rates for IR hepatitis [25]. More robust data are warranted on this topic, particularly on potential predictors for IR hepatitis.

To our knowledge, this is the first report of a metastatic HCC with a 5-year sustained response to nivolumab monotherapy. ICI is now standard treatment in HCC. Our patient experienced a significant response to nivolumab monotherapy, intriguingly following iatrogenesis and early ICI interruption, which not only questions the circumstances in which toxicity can translate to efficacy, but ulteriorly the rationale for advocating a standardized duration for anti-PD-1 exposure.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This publication did not require ethical approval as per local laws.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

José Leão Mendes, MD: conceptualization, investigation, visualization, and writing – original draft, review, and editing; Ana Sofia Spencer, MD: conceptualization, visualization, and writing – original draft, review, and editing; João Cabral Pimentel, MD: conceptualization, resources, and writing – review and editing; Mariana Sardinha, MD, João Boavida Ferreira, MD, and Ricardo da Luz, MD: supervision and writing – review and editing.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

References

1 Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63. https://doi.org/10.3322/caac.21834

2 Toh MR, Wong EYT, Wong SH, Ng AWT, Loo LH, Chow PKH, et al. Global epidemiology and genetics of hepatocellular carcinoma. Gastroenterology. 2023;164(5):766–82. https://doi.org/10.1053/j.gastro.2023.01.033

3 Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. J Hepatol. 2020;72(2):250–61. https://doi.org/10.1016/j.jhep.2019.08.025

4 Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int. 2015;35(9):2155–66. https://doi.org/10.1111/liv.12818

5 Ducreux M, Abou-Alfa GK, Bekaii-Saab T, Berlin J, Cervantes A, de Baere T, et al. The management of hepatocellular carcinoma. Current expert opinion and recommendations derived from the 24th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2022. ESMO Open. 2023;8(3):101567. https://doi.org/10.1016/j.esmoop.2023.101567

6 Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76(3):681–93. https://doi.org/10.1016/j.jhep.2021.11.018

7 Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid. 2022;1(8):EVIDoa2100070. https://doi.org/10.1056/EVIDoa2100070

8 Kudo M, Matilla A, Santoro A, Melero I, Gracián AC, Acosta-Rivera M, et al. CheckMate 040 cohort 5: a phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. J Hepatol. 2021;75(3):600–9. https://doi.org/10.1016/j.jhep.2021.04.047
9 FDA. Silver Spring (MD): FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib; 2018. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-hcc-previously-treated-sorafenib
10 Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Correction to: "hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(5):871–3. https://doi.org/10.1093/annonc/mdy510
11 Zhou JM, Xiong HF, Chen XP, Zhang ZW, Zhu LP, Wu B. Correlation between immune-related adverse events and long-term outcomes in pembrolizumab-treated patients with unresectable hepatocellular carcinoma: a retrospective study. World J Gastrointest Oncol. 2023;15(4):689–99. https://doi.org/10.4251/wjgo.v15.i4.689
12 Amoroso V, Gallo F, Alberti A, Paloschi D, Ferrari Bravo W, Esposito A, et al. Immune-related adverse events as potential surrogates of immune checkpoint inhibitors' efficacy: a systematic review and meta-analysis of randomized studies. ESMO Open. 2023;8(2):100787. https://doi.org/10.1016/j.esmoop.2023.100787
13 Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76(4):862–73. https://doi.org/10.1016/j.jhep.2021.11.030
14 Bicer F, Kure C, Ozluk AA, El-Rayes BF, Akce M. Advances in immunotherapy for hepatocellular carcinoma (HCC). Curr Oncol. 2023;30(11):9789–812. https://doi.org/10.3390/curroncol30110711
15 Longo V, Brunetti O, D'Oronzo S, Ostuni C, Gatti P, Silvestris F. Bone metastases in hepatocellular carcinoma: an emerging issue. Cancer Metastasis Rev. 2014;33(1):333–42. https://doi.org/10.1007/s10555-013-9454-4
16 Desai A, Sandhu S, Lai JP, Sandhu DS. Hepatocellular carcinoma in non-cirrhotic liver: a comprehensive review. World J Hepatol. 2019;11(1):1–18. https://doi.org/10.4254/wjh.v11.i1.1
17 Sakhuja P. Pathology of alcoholic liver disease, can it be differentiated from nonalcoholic steatohepatitis? World J Gastroenterol. 2014;20(44):16474–9. https://doi.org/10.3748/wjg.v20.i44.16474
18 Reig M, Cabibbo G. Antiviral therapy in the palliative setting of HCC (BCLC-B and -C). J Hepatol. 2021;74(5):1225–33. https://doi.org/10.1016/j.jhep.2021.01.046
19 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–73. https://doi.org/10.1016/S0140-6736(18)30207-1
20 Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2022;23(1):77–90. https://doi.org/10.1016/S1470-2045(21)00604-5
21 Galle PR, Decaens T, Kudo M, Qin S, Fonseca L, Sangro B, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs lenvatinib (LEN) or sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC): first results from CheckMate 9DW. J Clin Oncol. 2024;42(17_Suppl l):LBA4008. https://doi.org/10.1200/jco.2024.42.17_suppl.lba4008
22 Qin R, Jin T, Xu F. Biomarkers predicting the efficacy of immune checkpoint inhibitors in hepatocellular carcinoma. Front Immunol. 2023;14:1326097. https://doi.org/10.3389/fimmu.2023.1326097
23 Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(12):1217–38. https://doi.org/10.1016/j.annonc.2022.10.001
24 Riveiro-Barciela M, Barreira-Díaz A, Callejo-Pérez A, Muñoz-Couselo E, Díaz-Mejía N, Díaz-González Á, et al. Retreatment with immune checkpoint inhibitors after a severe immune-related hepatitis: results from a prospective multicenter study. Clin Gastroenterol Hepatol. 2023;21(3):732–40. https://doi.org/10.1016/j.cgh.2022.03.050
25 Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, et al. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. JAMA Oncol. 2020;6(6):865–71. https://doi.org/10.1001/jamaoncol.2020.0726