case report

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Immune-related hepatitis in a patient with hepatocellular carcinoma treated with nivolumab

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Summary We present a case of a male patient with advanced hepatocellular carcinoma who developed hepatic and dermatological immune-related adverse events during treatment with the immune checkpoint inhibitor nivolumab. We discuss relevant aspects regarding the management of immune-related hepatic adverse events, including the incidence and onset of the event, the requirement for immune-modulating medication, resuming of immunotherapy, and the association between the occurrence of immune-related adverse events and the outcome.

Keywords Immune-related hepatitis · Lichen ruber · Immunotherapy · Liver cancer

Case presentation

A 61-year-old male patient with alcoholic liver cirrhosis and a history of transjugular intrahepatic portosystemic shunt (TIPS) placement for refractory ascites underwent surveillance for hepatocellular carcinoma (HCC) with ultrasound at 6-month intervals at our institution. When ultrasound showed a new onset of portal vein thrombosis, the patient was referred for a computed tomography (CT) scan. The CT scan revealed a 6-cm tumor with portal vein invasion, several smaller hypodense liver lesions, and no clear evidence of extrahepatic metastases. Biopsy finally confirmed the diagnosis of moderately differentiated HCC. The tumor marker alpha-fetoprotein was within the normal range at this time. Based on a well-preserved liver function (Child–Pugh class A), a performance status of 0 (asymptomatic), and vascular tumor invasion, the patients was classified as having advanced-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage C).

After multidisciplinary team discussion, systemic treatment was recommended and the immune checkpoint inhibitor (ICI) nivolumab at a dose of 240 mg every 2 weeks was initiated. After the second cycle, a grade 3 increase in transaminases was noted (Fig. 1). The patient was asymptomatic and had no signs of liver decompensation. Given the rapid increase, immune-related hepatitis (irHepatitis) was suspected. Nivolumab was paused and prednisolone was initiated with an intravenous bolus of 0.75 mg/kg followed by a maintenance dose of 50 mg daily. After 1 week, the transaminase levels decreased significantly and prednisolone was tapered over a 4-week course. However, after discontinuation of prednisolone, an increase in transaminases was noted again and prednisolone was reinitiated at a dose of 50 mg daily for 2 weeks and then tapered over a course of 3 weeks. The transaminase levels eventually returned to normal values and nivolumab treatment was finally resumed around 3 months after initiation of steroids. Despite the 3-month interruption of nivolumab treatment, the patients achieved stable disease on follow-up imaging and remained stable for 2.5 years. He never developed an episode of irHepatitis again during this period.

However, approximately 1 year after the start of nivolumab treatment, the patient developed scaly, psoriasiform skin lesions on the upper and lower extremities (Fig. 2). After histological evaluation, the diagnosis of an immune-mediated verrucous lichen ruber was made. Given that the lichen was complicated by recurrent skin infections, the patient repeatedly received antibiotic treatment and nivolumab

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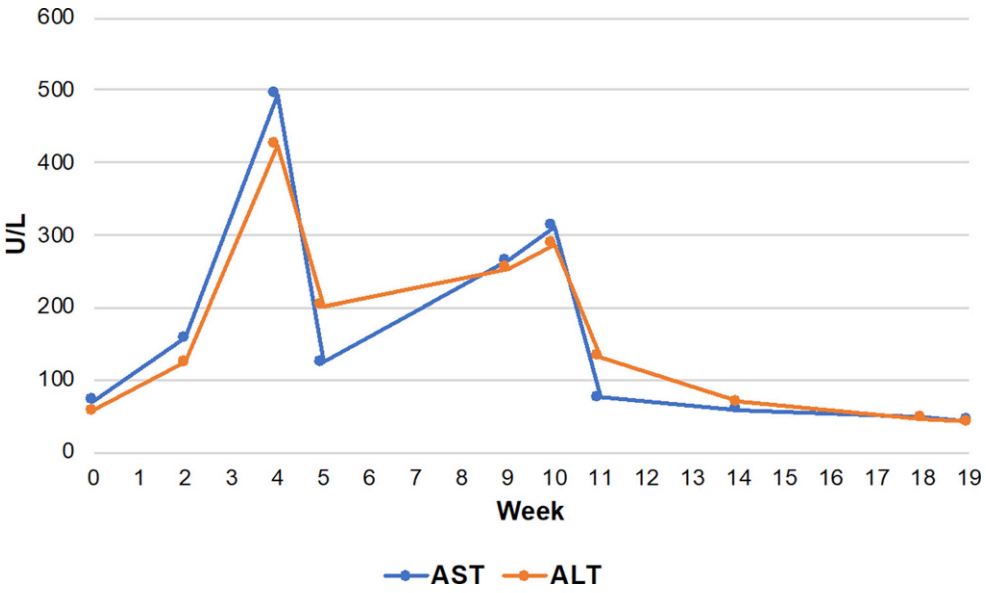

Fig. 1 Course of transaminases. At week 4 after initiation of nivolumab, the patient experienced a grade 3 increase in transaminases (upper limit of normal is <50 U/l for both AST and ALT). Nivolumab was paused and treatment with prednisolone was initiated at a dose of 50 mg daily. After steroid tapering, the transaminase levels increased again at week 9, which prompted a new escalation of the prednisolone dose to 50 mg daily for 2 weeks. Steroids were then tapered over a 3-week course and transaminase levels eventually returned to normal values. Nivolumab was restarted at week 17. *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

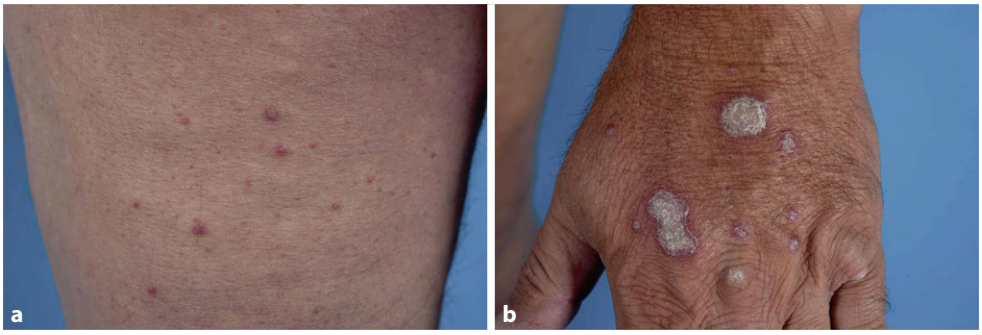

Fig. 2 Lichenoid skin lesions. Around 1 year after initiation of nivolumab treatment, the patient developed scaly, psoriasiform skin lesions on the upper and lower extremities. The diagnosis of an immune-mediated verrucous lichen ruber was made after histological evaluation

treatment was interrupted several times. The skin lesions were treated with topical steroids and photochemotherapy (PUVA).

Around 3 years after initiation, nivolumab was discontinued due to tumor progression. Thereafter, the patient received several lines of systemic therapy, including sorafenib, lenvatinib, cabozantinib, and regorafenib, and died roughly 1 year later due to further tumor progression.

Discussion

Several systemic therapies are approved for the treatment of patients with HCC, including sorafenib and lenvatinib in first-line treatment, and regorafenib, cabozantinib, and ramucirumab in patients pretreated with sorafenib. Immunotherapy has been added to the treatment armamentarium only recently [1]. The immune checkpoint inhibitors nivolumab, pembrolizumab, and the combination of nivolumab plus ipilimumab have been conditionally approved based on promising data from phase II trials in the United States (but not in Europe; [1, 2]). The combination of atezolizumab and bevacizumab improved overall survival and progression-free survival over sorafenib in a phase III trial [3], and represents the new reference standard in systemic front-line therapy of HCC [1].

Immune-related adverse events of immune checkpoint inhibitors can affect several organs, including the liver. Immune-related hepatic adverse events usually occur within 4–12 weeks of immunotherapy initiation. They affect approximately 5–10% of patients treated with monotherapy, but are much more frequent upon combination of ICIs (15–30%). During diagnostic work-up, differential diagnoses (i.e., intrahepatic tumor progression, hepatotoxic medication, acute viral infection or flares in patients with chronic

viral hepatitis, alcohol abuse, thrombotic events or benign biliary obstructions) need to be excluded [4–7]. Notably, in patients developing an increase in liver enzymes during ICI treatment, immune-related hepatic adverse events were diagnosed in only 16% of cases, while around half of the patients had tumor progression [8].

In our patient, a grade 3 increase in transaminase levels developed 4 weeks after nivolumab initiation. Given the rapid onset and the low likelihood of other potential causes, we suspected irHepatitis. The good response to steroid treatment eventually confirmed the diagnosis. The adverse event was resolved around 3 months after steroid initiation. This is well in line with previous reports on the management of immune-related hepatic adverse events in patients with HCC receiving nivolumab [9]. Of 37 patients experiencing hepatic adverse events, seven (19%) required systemic corticosteroids and only one patient (3%) required additional mycophenolic acid. Resolution of the event occurred in all seven patients (100%) requiring immune-modulating medication after a median time of 19.4 weeks [9].

According to current recommendations, PD-(L)1-targeted ICIs can be resumed in cases of grade 3 irHepatitis while permanent discontinuation is recommended in patients experiencing grade 4 irHepatitis [4]. In our patient, nivolumab was resumed when steroids were discontinued and transaminases returned to baseline values. Even though our patient received nivolumab for more than 2 years, he never developed an episode of irHepatitis again. However, the further course of treatment was complicated by lichen ruber, a known but rather rare dermatological adverse event during ICI treatment, [10] that occurred approximately 1 year after nivolumab initiation.

The occurrence of immune-related adverse events may be associated with improved outcomes in cancer patients treated with ICIs [11–13], and this association could be even more pronounced in patients with multisystem immune-related adverse events [14]. Our patient, who experienced two immune-related adverse events, failed to respond to treatment but achieved stable disease for over 2 years, which can be considered treatment success.

Conclusion

Immune-related hepatic adverse events usually occur early after ICI initiation, sometimes require systemic corticosteroids, but rarely additional immune-modulating medication, and mostly resolve within several weeks of initiation of immunomodulators [4, 9].

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