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Case report

UNUSUALLY LATE SPINAL CORD METASTASIS OF HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related mortality worldwide. Liver transplantation (LT) is a curative option for selected patients; however, recurrence remains the major determinant of post-transplant survival. Most recurrences occur within the first five years, while ultra-late events are exceptionally rare.

We describe a 66-year-old male with cirrhosis due to hereditary hemochromatosis and a solitary 4-cm HCC within the Milan criteria, who underwent cadaveric orthotopic LT after bridging therapy with a single session of transarterial chemoembolization. Explant pathology confirmed HCC without microvascular invasion. The postoperative course was uneventful, and the patient remained disease-free for thirteen years. He then presented with rapidly progressive bilateral paraparesis. Magnetic resonance imaging revealed a 30-mm intradural extramedullary lesion at T6 causing severe spinal cord compression. Neurosurgical resection was performed, and histopathology with immunohistochemistry (HepPar-1 positive) confirmed metastatic HCC.

This is, to our knowledge, the first reported case of spinal cord metastasis from HCC occurring thirteen years after LT. Conventional tumor markers, including alpha-fetoprotein, remained within normal limits, underscoring the limitations of current surveillance protocols. The exceptionally prolonged disease-free interval and atypical metastatic site challenge the prevailing paradigm that follow-up can be safely limited to the early post-transplant years. Ultra-late recurrence of HCC after LT, though rare, is clinically relevant and may manifest in unusual sites. This case highlights the need for risk-stratified, individualized, and potentially extended surveillance strategies to optimize long-term outcomes in LT recipients.

Key words: carcinoma, hepatocellular, neoplasm metastasis, liver transplantation, spinal cord

Resumen

Metástasis medular inusualmente tardía de carcinoma hepatocelular después de trasplante hepático

El carcinoma hepatocelular (CHC) es el cáncer primario más frecuente del hígado. El trasplante hepático (TH) constituye un tratamiento curativo en pacientes seleccionados; sin embargo, la recurrencia sigue siendo el principal determinante de la supervivencia postrasplante.

Se describe el caso de un hombre de 66 años con cirrosis secundaria a hemocromatosis hereditaria y un CHC solitario de 4 cm dentro de los criterios de Milán, sometido a trasplante hepático ortotópico cadavérico tras terapia de puente con una sesión de quimioem-

bolización transarterial. La anatomía patológica del explante confirmó CHC sin invasión microvascular. La evolución postoperatoria fue favorable y el paciente permaneció libre de enfermedad durante trece años. Posteriormente, consultó por paraparesia bilateral rápidamente progresiva. La resonancia magnética evidenció una lesión intradural extramedular de 30 mm a nivel de T6 con compresión medular grave. Se realizó resección neuroquirúrgica, y el estudio histopatológico con inmunohistoquímica (HepPar-1 positivo) confirmó metástasis de CHC.

Este constituye, a nuestro conocimiento, el primer caso reportado de metástasis medular de CHC trece años después de un TH. Los marcadores tumorales convencionales, incluido el alfa-fetoproteína, se mantuvieron en rango normal, lo que evidencia las limitaciones de los protocolos de vigilancia actuales. El intervalo libre de enfermedad extraordinariamente prolongado y la localización atípica cuestionan la noción de que el seguimiento pueda restringirse a los primeros años. La recurrencia ultra-tardía de CHC tras TH, aunque infrecuente, es clínicamente relevante y puede presentarse en sitios inusuales. Este caso resalta la necesidad de estrategias de seguimiento individualizadas, estratificadas por riesgo y posiblemente extendidas en el tiempo.

Palabras clave: carcinoma hepatocelular, metástasis de la neoplasia, trasplante de hígado, médula espinal.

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver and a major global health burden[1,2]. Liver cirrhosis is the principal risk factor for HCC and represents the leading cause of death among cirrhotic patients[3]. Worldwide, HCC is the second leading cause of cancer-related mortality, responsible for approximately 750 000 deaths annually, with therapeutic strategies still limited[4].

Liver transplantation (LT) is a well-established curative treatment for selected HCC patients, offering the dual benefit of removing the tumor and addressing the underlying liver disease[2]. Nevertheless, post-transplant recurrence occurs in 5%-30% of cases[4]. When recurrence develops, it is most often detected within the first one to two years after LT, with the majority (67%) involving extrahepatic metastases to the lung, bone, adrenal gland, peritoneal lymph nodes, or brain[4-6].

Although complete prevention of recurrence is not feasible, post-transplant surveillance remains essential. The optimal duration and interval of follow-up, however, are debated, as most recurrences occur within the first few years after LT and very late recurrences-beyond five years are rare. Given this low incidence, some authors have argued that prolonged surveillance may not be cost-effective[7].

Patients with HCC recurrence after liver transplantation (LT) were classified into three groups based on the timing of recurrence: Group 1, early recurrence (within the first year); Group 2, late recurrence (between years 2 and 5); and Group 3, very late recurrence (beyond 5 years)[8].

The authors present a case of intramedullary spinal cord metastasis from hepatocellular carcinoma occurring 13 years after deceased-donor liver transplantation.

Clinical case

A 66-year-old male with a history of decompensated cirrhosis secondary to hereditary hemochromatosis, complicated by hepatocellular carcinoma, underwent cadaveric orthotopic liver transplantation. In the pre-transplant setting, he received a single session of transarterial chemoembolization (TACE) as bridging therapy, aimed at maintaining tumor stability and preventing disease progression while awaiting transplantation. This strategy was particularly justified by the presence of a solitary 4-cm lesion within the Milan criteria.

Cross-sectional imaging demonstrated a 4 cm nodule with arterial phase contrast enhancement and early venous washout, radiological features consistent with HCC. These findings were confirmed by two independent imaging modalities computed tomography (CT) and magnetic resonance imaging (MRI) in accordance with transplant evaluation protocols, Given the prolonged time since the liver transplantation, the corresponding CT and MRI images are no longer accessible for documentation. Preoperative serum alpha-fetoprotein (AFP) was 100 ng/mL.

The liver transplantation was performed uneventfully, and the patient experienced an uncomplicated postoperative recovery, being discharged in good general condition. The liver transplantation proceeded without complications, and the patient had an uneventful postoperative recovery, being discharged in good clinical condition. Explant examination demonstrated a solitary 4-cm hepatocellular carcinoma without microvascular invasion, fully consistent with the Milan criteria, and no additional tumor foci or satellite nodules were identified. His long-term immunosuppressive regimen consisted of tacrolim-

us at a daily dose of 6 mg, with stable therapeutic trough levels. Following transplantation, hereditary hemochromatosis was managed through routine surveillance with serial iron studies; phlebotomy was not required, as iron parameters remained stable and no biochemical or clinical evidence of recurrent iron overload was observed. The postoperative course was uneventful, and the patient remained clinically stable for thirteen years. During this period, AFP levels showed a gradual increase, although values remained within the normal range. He presented with a three-day history of rapidly progressive bilateral lower-limb paraparesis. His functional status deteriorated from full independence to requiring a walker for ambulation. He reported no sensory deficits or sphincter disturbances. Urgent spinal magnetic MRI demonstrated a 30-mm intradural extramedullary solid mass at the T6 level with homogeneous gadolinium enhancement, causing obliteration of the perimedullary spaces and marked spinal cord compression (Fig. 1).

Postoperatively, the patient showed progressive neurological improvement and remains in rehabilitation, without evidence of new lesions or disease progression.

The patient underwent neurosurgical intervention with complete excision of the lesion. Histopathological examination revealed a tumor composed of osseous tissue, hyaline cartilage, and fibrous stroma infiltrated by a predominantly solid neoplastic proliferation. Tumor cells exhibited abundant eosinophilic cytoplasm, round prominent nuclei, variable atypia, and evident mitotic activity. Immunohistochemical staining was strongly positive for HepPar-1 and AE1/AE3, confirming the diagnosis of metastatic hepatocellular carcinoma (Fig. 2).

Written informed consent was obtained from the patient for publication of this case and accompanying images.

Discussion

Hepatocellular carcinoma is the most common primary liver cancer worldwide[1]. The risk of post-transplant HCC recurrence is a major concern in LT recipients as it is the most common cause of patient death. The risk of recurrence increases with broader LT eligibility criteria; therefore, prudent selection of LT candidates is important to reduce the risk of post-transplant HCC recurrence[8,9]. Post-transplant HCC recurrence was predominantly characterized by distant metastases, most frequently involving the

Figure 1 | Magnetic resonance imaging revealed a 30-mm intradural extramedullary solid mass at the D6 level, showing homogeneous gadolinium enhancement. The lesion resulted in obliteration of the perimedullary spaces and significant compression of the spinal cord

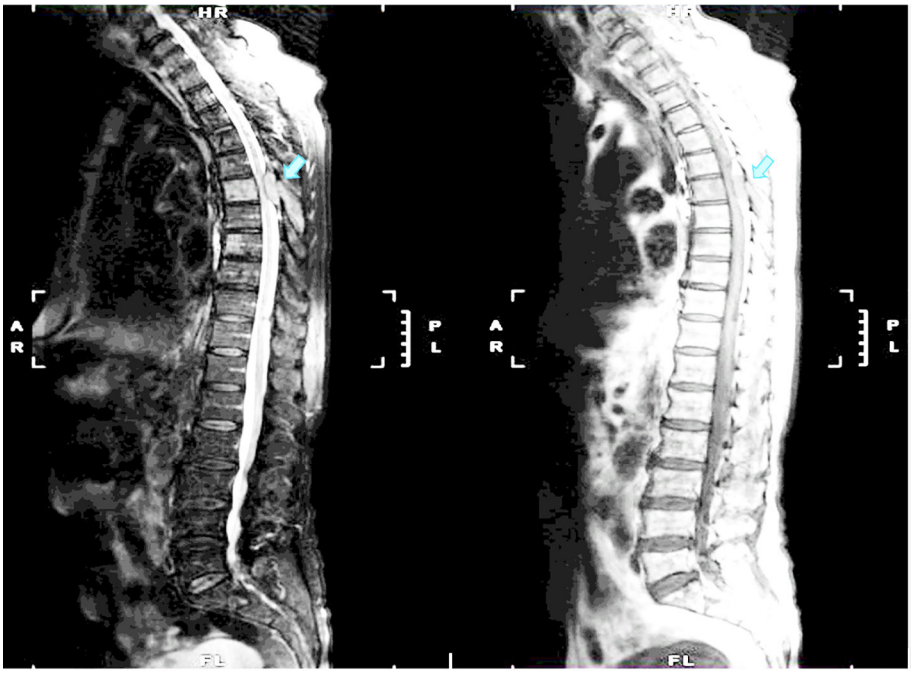
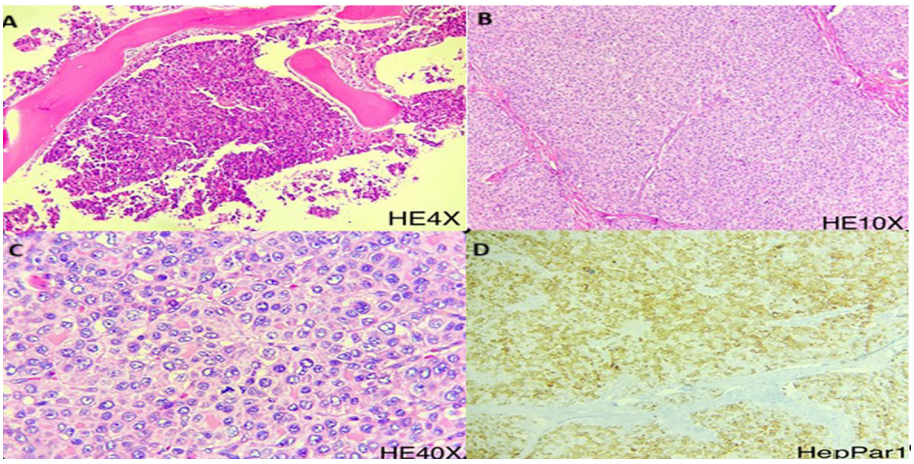


Figure 2 | A: HE4X: Infiltration of the bone marrow by an epithelial proliferation with trabecular and solid growth pattern is observed, composed of polygonal cells with eosinophilic cytoplasm and pleomorphic nuclei with prominent nucleoli. B: HE10X: Epithelial neoplastic proliferation with trabecular and pseudoglandular patterns, composed of polygonal cells exhibiting abundant eosinophilic cytoplasm, rounded nuclei with vesicular chromatin, and conspicuous nucleoli. The tumor cells are arranged in thick trabeculae surrounded by vascular sinusoids. C: HE40X: Proliferation of polygonal neoplastic cells with eosinophilic cytoplasm and pleomorphic nuclei, displaying frequent mitotic figures; D: Immunohistochemistry: Tumor cells demonstrate strong cytoplasmic positivity for Hepar-1, confirming hepatocellular origin



lungs and bones, whereas isolated intrahepatic recurrence was less common[7].

Blood AFP measurement is a simple test that can be performed along with other routine laboratory tests during outpatient clinic visits. In patients who had overexpression of AFP prior to LT, there is a high probability of AFP elevation at the time of HCC recurrence[6,8]. Therefore, AFP testing should be performed routinely at outpatient clinic visits. PIVKA-II, another serum tumor marker of HCC, has a complementary role in the diagnosis of HCC, although its sensitivity and specificity are lower than those of AFP[7,10,11]. In our case, despite routine monitoring, serum AFP levels remained within normal ranges, failing to predict recurrence. This finding highlights the limitation of relying solely on conventional tumor markers for post-transplant surveillance and underscores the need for more specific and sensitive biomarkers to accurately detect late or atypical patterns of hepatocellular carcinoma recurrence.

To the best of our knowledge, this is the first reported case of distant spinal cord metastasis from HCC occurring thirteen years after liver transplantation. Alshahrani et al[12] described two cases of late-onset distant metastases following transplantation, at ten and twelve years, involving the transverse colon and pelvis, respectively. Hostalot et al[13]. reported a case of spinal cord compression due to HCC metastasis; however, that patient had not received prior treatment for the primary tumor.

The occurrence of very late hepatocellular carcinoma (HCC) recurrence in the form of spinal cord metastasis thirteen years after liver transplantation is an exceptionally rare event that challenges the current understanding of post-transplant tumor biology. Such an unusually prolonged disease-free interval, together with the atypical metastatic site, underscores the limitations of conventional surveillance strategies that typically emphasize early recurrence. This case highlights the importance of risk-stratified, individualized follow-up protocols, which may provide greater clinical benefit than standardized, short-term approaches. Ultimately, multicenter collaborative studies are needed to better define the biological determinants of ultra-late recurrence and to establish evidence-

based criteria for extended surveillance in liver transplant recipients.

Histopathological and immunohistochemical findings confirmed that the lesion corresponded to a metastasis from hepatocellular carcinoma rather than a primary spinal cord tumor. The trabecular and pseudoglandular epithelial growth pattern, together with the strong cytoplasmic positivity for Hepar-1, unequivocally established the hepatocellular origin of the neoplasm, thereby excluding the possibility of a primary central nervous system tumor.

Conflict of interest: None to declare

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