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Letter to the Editor

Late Recurrence of Lymph Node Micro-Metastatic Hepatoblastoma Following Living Donor Liver Transplantation

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Dear Editor,

Hepatoblastoma (HB) is the most common primary liver malignancy in childhood, and liver transplantation (LT) is the main curative treatment option in unresectable cases. The overall 5-year survival rate after LT is approximately 70%. According to the SIOPEL risk stratification, the presence of lymph node involvement and/or metastatic disease classifies patients as high-risk; approximately 20% of HB patients present with locally advanced or metastatic disease at diagnosis.[1,2] Recurrence after LT for HB is defined as biopsy-proven or radiologically confirmed mass lesions accompanied by three consecutive rises in serum alpha-fetoprotein (AFP) levels. Late recurrence is extremely rare and has been reported in only two separate cases in the literature.[3,4] Herein, we present a patient who underwent living donor liver transplantation (LDLT) at the age of six for unresectable HB, with lymph node (LN) micro-metastasis and local peritoneal invasion identified in the explant pathology, who developed recurrence 4.5 years post-transplant and survived more than five years post-LT.

A male patient presenting with abdominal distention was referred to our center for LT after receiving five cycles of cisplatin and doxorubicin for unresectable HB, achieving stable disease and classified as POSTTEXT stage III.[5] Upon admission, biochemical parameters were within normal limits, and AFP was 2615 ng/mL. LDLT was successfully performed using the donor's (20-year-old brother) left lateral segment (segments 2–3). The donor was discharged uneventfully on postoperative day 9. On postoperative day 2, the recipient developed hepatic artery thrombosis, necessitating urgent surgical revision; however, graft failure ensued, and emergency retransplantation with a reduced-size deceased donor graft (segments 2–3) was performed on postoperative day 5. The patient was discharged on postoperative day 37. Explant pathology revealed three foci (up to 5 cm) of epithelial-type HB. Of five lymph nodes dissected from the hepatic hilum, one contained a microscopic HB focus, and an additional microscopic HB lesion was identified in Gerota's fascia adjacent to an exophytic segment 5 lesion extending toward the kidney (Fig. 1). Based on these findings, adju-

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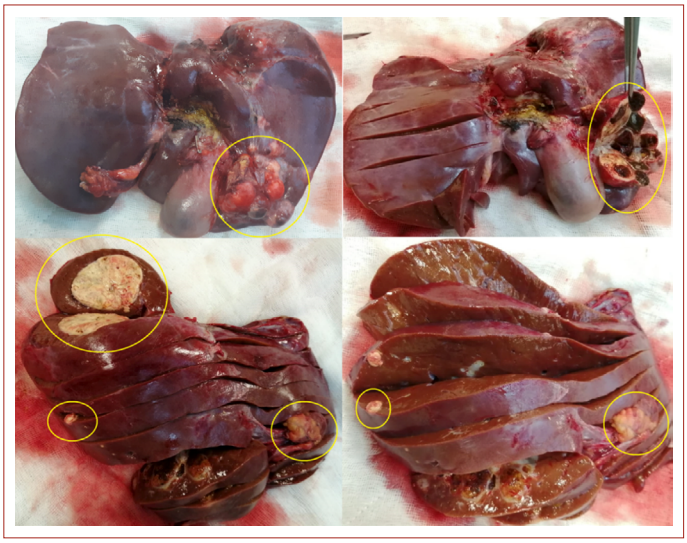

Figure 1. Explant specimen.

vant chemotherapy (etoposide + ifosfamide + carboplatin) was administered for two cycles due to advanced-stage/metastatic disease. Post-LT AFP remained within normal limits for two years but then showed mild elevation (AFP: 20 ng/mL; normal <9 ng/mL). Thoracic CT, abdominal CT, cranial MRI, and FDG PET-CT revealed no pathology. Viral serology demonstrated positivity for HBsAg, HBeAg, and HBV DNA, leading to a diagnosis of de novo HBV hepatitis; antiviral therapy with lamivudine was initiated, and the mild AFP elevation was attributed to HBV infection. During the following 2.5 years, no pathological finding was detected, and AFP fluctuated between 20–63 ng/mL. At 4.5 years post-LT, AFP abruptly increased to 918 ng/mL (from 63 ng/mL six months earlier). Imaging studies showed no metastatic lesions, though HBV DNA remained positive, and antiviral therapy was switched to tenofovir. Preemptive chemotherapy was not initiated. Three months later, AFP rose further to 6244 ng/mL, and imaging revealed multiple hepatic and left pulmonary metastatic lesions (Fig. 2). The multidisciplinary tumor board recommended systemic therapy; however, the patient developed massive ascites and hepatic decompensation, requiring palliative management. The patient died at 64 months post-LT (5.3 years) due to tumor recurrence.

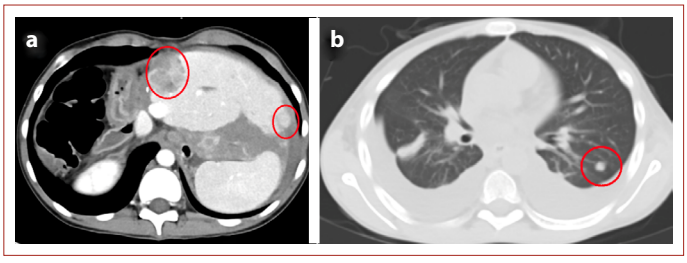

Figure 2. (a) Recurrences on the transplanted liver, **(b)** Lung metastases.

Overall and disease-free survival rates following LT for HB—whether performed as primary (pLT) or salvage LT (sLT)—exceed 60% at five years. In a study by Umeda et al., the 5-year overall survival was 69% for pLT and 73% for sLT, while Boster JM et al. reported 5-year disease-free survival rates of 78% for pLT and 62% for sLT. Thus, LT achieves favorable long-term outcomes for HB. Our patient underwent LT despite advanced-stage disease with lymph node metastasis and local invasion. Remarkably, no recurrent lesions were detected for 4.5 years post-transplant. AFP increased sharply thereafter, and hepatic and pulmonary metastases became radiologically visible once AFP exceeded 6000 ng/mL. During the period of rising AFP, persistent HBsAg, HBeAg, and HBV DNA positivity (under tenofovir therapy) suggested ongoing HBV replication. This raises the possibility that HBV reactivation might have triggered tumor cell proliferation.

Similarly, we previously observed a comparable scenario in a patient with hepatocellular carcinoma who exhibited unexplained AFP elevation post-LT without detectable recurrence on CT or PET-CT. Brain metastasis was subsequently discovered when the patient presented with neurological symptoms highlighting the limited sensitivity of PET-CT for detecting cerebral metastases and the importance of conventional cranial imaging in such cases. [6] In the current case, despite comprehensive imaging including cranial and genitourinary evaluations—no lesion was detected until AFP exceeded 6000 ng/mL. The gradual AFP rise (20–63 ng/mL) over 2.5 years, followed by a rapid increase to 918 ng/mL in six months and 6244 ng/mL within three months, correlated with detectable recurrence. We speculate that HBV replication and immunosuppressive therapy may have jointly promoted tumor progression. Bandopadhyay et al. previously demonstrated that the hepatitis B virus X protein (HBx) can contribute to hepatoblastoma carcinogenesis by suppressing miR-122 expression in HB cells,[7] supporting our hypothesis. Moreover, we believe that adjuvant chemotherapy administered post-transplantation may have contributed to delaying early recurrence.

In conclusion, during follow-up of HB patients after LT, both rapid and gradual increases in AFP should be considered potential indicators of tumor recurrence or metastasis, even in the absence of radiologically detectable lesions. Conventional imaging modalities may fail to identify early recurrence. Although data are insufficient to support preemptive adjuvant chemotherapy, given the propensity for microinvasion and metastatic spread, post-LT adjuvant chemotherapy protocols may warrant reevaluation.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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