Case Report

Renal metastasis of hepatocellular carcinoma after living donor liver transplantation

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Abbreviations & Acronyms
AFP = alpha-fetoprotein
CT = computed tomography
HCC = hepatocellular carcinoma
LT = liver transplantation
mPSL = methylprednisolone
PIVKA-II = protein induced by vitamin K absence II
POM = postoperative month

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Introduction: We report a case of renal metastasis of hepatocellular carcinoma in a liver transplant recipient.

Case presentation: A 66-year-old man who was diagnosed with hepatocellular carcinoma and considered to be in complete remission for 7 years underwent living donor liver transplantation. A residual tumor was found in the removed native liver. Computed tomography at 13 months after transplantation revealed a 24-mm hypervascular tumor with arterial phase enhancement, venous phase washout in the right kidney, and increasing hepatocellular carcinoma tumor markers. Partial nephrectomy was performed and the renal tumor was diagnosed as renal metastasis of hepatocellular carcinoma. Tumor marker levels decreased temporarily, but pulmonary metastasis and pleural dissemination subsequently appeared.

Conclusion: Renal metastasis of hepatocellular carcinoma should be considered when renal tumors are detected in liver transplant recipients because the risks of tumor recurrence and metastasis are increased.

Key words: hepatocellular carcinoma, kidney neoplasms, liver transplantation, partial nephrectomy, renal metastasis.

Keynote message

Renal metastasis of HCC is rare after LT. However, the possibility of renal metastasis should be considered when a renal mass and increased tumor marker levels are detected in patients with HCC who underwent LT. If renal metastasis is diagnosed early, then surgical resection could control disease progression.

Introduction

Common sites of primary tumor associated with renal metastasis are lung, colon, and head and neck as well as renal metastasis of HCC are rare.[1,2] Common sites of HCC recurrence and metastasis after LT include the transplanted liver, lungs, bones, adrenal glands, and peritoneum.[3] We report a case of a liver transplant recipient diagnosed with residual HCC in the removed liver and renal metastasis of HCC detected at 13 months after LT.

Case presentation

Contrast-enhanced CT revealed a potential right renal tumor in a 66-year-old male patient who underwent living donor LT 13 months before presentation to our department. HCC had been diagnosed 14 years previously; therefore, he had undergone arterial embolization therapy. Intrahepatic recurrences were treated 11, 10, and 8 years previously. CT and fluoro-2-deoxyglucose positron emission tomography did not reveal tumor recurrence or metastasis during the 7-year interval. AFP and prothrombin induced by vitamin K absence II (PIVKA-II) levels were increased (467 ng/mL [normal range, <10 ng/mL] and 359 mAu/mL [normal

range, <40 mAu/mL], respectively). At that time, these high tumor marker levels were considered attributable to Child–Pugh class C liver cirrhosis, but not to HCC recurrence, because they remained largely unchanged and imaging evaluations did not detect any recurrence for a long period.

The patient underwent living donor LT because of decompensated liver cirrhosis caused by hepatitis B virus at our institute 1 year before presentation to our department. Residual HCC (55 mm) and venous invasion were detected in the removed liver (pT2N0). Tumor marker levels decreased to the normal range immediately after transplantation, but the AFP level began to increase 3 months later (Fig. 1). Immunosuppressive therapy comprising tacrolimus and methylprednisolone was initiated. However, because HCC recurrence was possible, tacrolimus was discontinued and everolimus 2 mg was initiated. Methylprednisolone was gradually reduced over the course of 6 months from 160 mg/day to 2 mg/day. Contrast-enhanced CT was performed every 3 months. At 13 months after LT, CT revealed a 24-mm hypervascular tumor with arterial phase enhancement and venous phase washout in the upper pole of the right kidney; therefore, he presented to our department (Fig. 2). The AFP and PIVKA-II levels increased to 437 ng/mL and 97 mAu/mL, respectively, and renal cell carcinoma and renal metastasis of HCC were suspected. The renal tumor was smaller than 4 cm, located at the upper pole and apart from the renal vessels; therefore, right open partial nephrectomy was performed the following month. A macroscopic examination revealed that the resected specimen contained a 20-mm solid white tumor covered by Gerota's fascia without obvious tumor exposure to the surgical margin (Fig. 3a). A histopathologic examination revealed a solid trabecular pattern of tumor cells with both clear and eosinophilic cytoplasm. Based on the histological similarity to primary HCC and immunohistochemical positivity for hepatocyte paraffin 1, the renal tumor was diagnosed as renal metastasis of HCC (Fig. 3b–d). Two months later, the AFP and PIVKA-II levels decreased to 119 ng/mL and 52 mAu/mL, respectively. At 6 months after partial nephrectomy, CT detected a 10-mm solitary nodule in the right lung and increased tumor marker levels, suggesting pulmonary metastasis. Video-assisted thoracoscopic surgery was performed immediately, and the histopathological diagnosis was lung metastasis of HCC. Two months later, pleural dissemination and increased tumor markers were detected. After initiating lenvatinib 8 mg/day, the tumor marker levels decreased. Close monitoring of treatment efficacy was continued.

Discussion

Renal metastasis of HCC is rare, with only 10 cases reported in the literature (Table 1). Only one previous case involved LT; therefore, ours is the second case of renal metastasis of HCC after LT. The previous case was 70-year-old male comprised 55-mm renal metastasis diagnosed 9 years after LT and sirolimus as immunosuppressive therapy. Radical nephrectomy was performed, but multiple lung metastases were detected 5 months later; therefore, sorafenib was initiated. It was unclear whether radical nephrectomy was superior to partial nephrectomy in terms of cancer

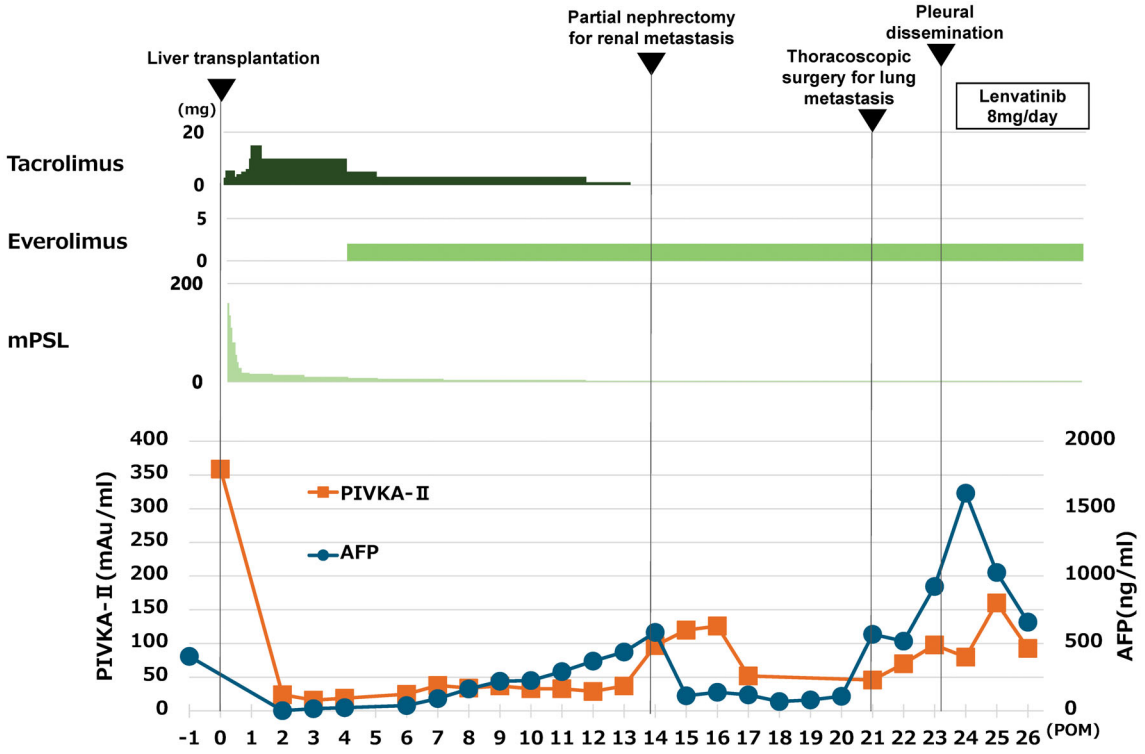

Fig. 1 Time course of tumor markers, immunosuppressive agents, and treatment after living donor liver transplantation.

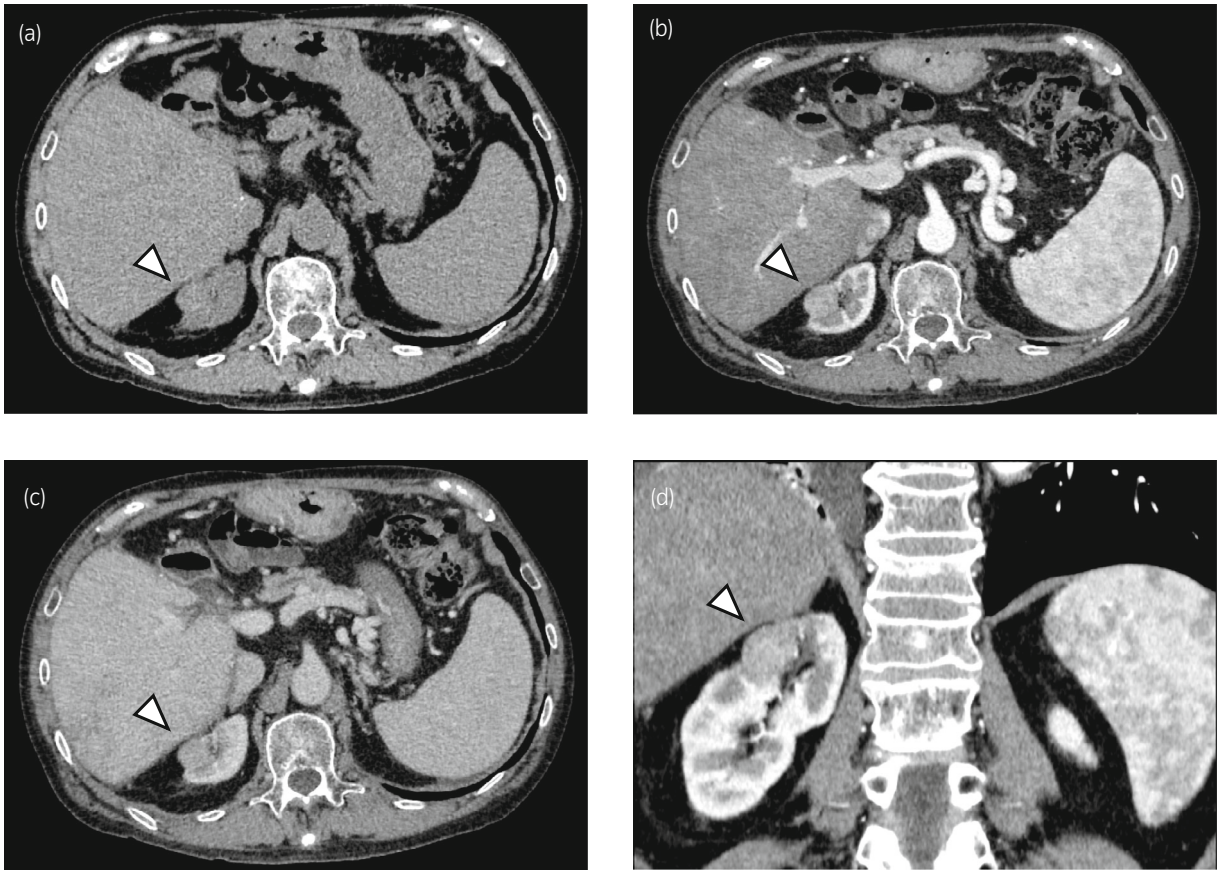

Fig. 2 Computed tomography (CT) images of the right kidney tumor (a: plain CT; b and d: arterial phase; c: venous phase). A 24 × 23-mm mass with arterial phase enhancement and venous phase washout (arrowheads) was detected in the upper pole of the right kidney.

control for metastatic renal rumors; therefore, in our patient, partial nephrectomy was selected, because of the tumor size and location. However, lung metastasis and pleural dissemination were observed 6 and 8 months after partial nephrectomy, respectively. Previous studies found that surgical resection of lung metastasis of HCC was effective, and that the efficacy of perioperative chemotherapy for metastasectomy of HCC is limited.[4,5] Additionally, immune checkpoint inhibitors, which are mainly used for systemic treatment of HCC, are associated with high risks of graft rejection and mortality for patients who have undergone LT.[6] Therefore, although lung metastases were detected 6 months later, partial nephrectomy was not considered an inappropriate choice.

HCC recurrence after LT has been observed in 6%–18% of patients, and 60% of recurrences occurred within 2 years.[7,8] Earlier recurrence is often associated with a worse prognosis.[7–9] Therefore, careful follow-up is recommended during the first 2 years to detect recurrence as early as possible.[10–12] CT evaluations were performed every 3 months because of the increasing AFP level in our patient, thus allowing an early diagnosis of renal metastasis.

Immunosuppressive agents can contribute to cancer development in organ transplant recipients.[13] Calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors are commonly used as immunosuppressive agents after LT. Calcineurin inhibitors can compromise cancer defense mechanisms and accelerate cancer progression; therefore, they are associated with tumor growth and metastasis.[14–16] In contrast, mTOR inhibitors have anti-proliferative and anti-angiogenic effects. Patients who have undergone LT for HCC and are using calcineurin inhibitors experienced higher tumor recurrence and lower overall survival rates compared with those of patients who are using mTOR inhibitors.[17] For our patient, immunosuppressive agents were changed from calcineurin inhibitors to mTOR inhibitors after the AFP level increased, which was a reasonable choice; however, renal metastasis was detected.

In conclusion, we temporarily controlled disease progression and tumor marker levels by performing partial nephrectomy. Although renal metastasis is rare, it should be considered for patients with HCC after LT.

Author contributions

Yo Nakamura: Conceptualization; data curation; visualization; writing – original draft. Jun Kamei: Conceptualization; methodology; project administration; writing – original draft. Ryo Tanaka: Writing – review and editing. Yoichi Yasunaga: Investigation; writing – review and editing. Nobuhisa Akamatsu: Methodology; writing – review and editing. Satoru Taguchi: Writing – review and editing; formal analysis. Shigenori Kakutani: Writing – review and editing. Yuta Yamada: Resources; writing – review and editing. Aya Niimi: Writing

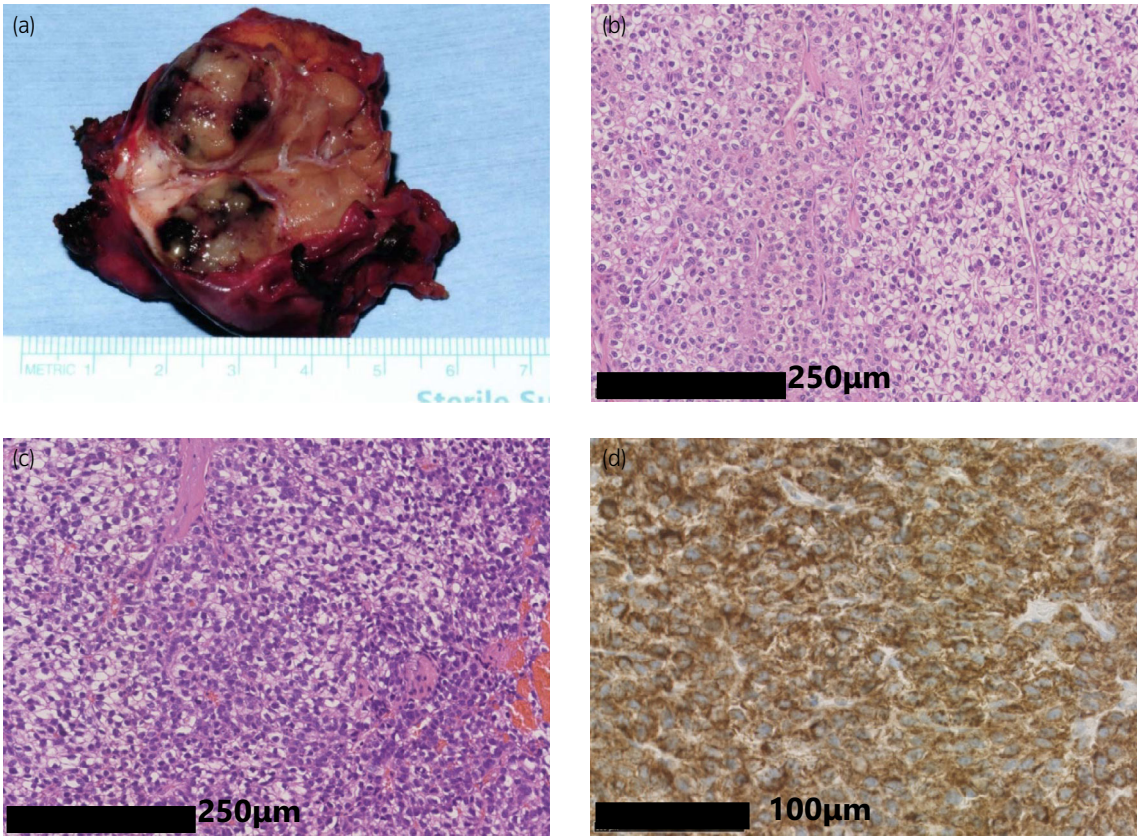

Fig. 3 Pathological findings. (a) Gross image of the right renal tumor. A solid white 20 × 20 × 15-mm tumor is on the cut surface. Histology of primary hepatocellular carcinoma (b) detected in the removed liver after liver transplantation and the renal tumor (c) (both hematoxylin & eosin, ×200), with both demonstrating a solid trabecular pattern comprising tumor cells with clear and eosinophilic cytoplasm. (d) Immunohistochemistry of hepatocyte paraffin 1 in the renal tumor with diffusely positive tumor cells.

Table 1 Characteristics of patients of renal metastasis of hepatocellular carcinoma previously reported with detail clinical information and our case

	Previous cases (n = 6)	Our case
Age, years, median (range)	70.5 (52–76)	66
Male	5 patients	Yes
Female	1 patient	No
Prior liver transplantation	1 patient	Yes
Maximum tumor diameter, mm, median (range)	67.5 (21–86)	24
Metastasis to organs other than the kidney		
No metastasis	4 patients	Yes
Brain metastasis	1 patient	No
Lung metastasis	2 patients	No
Treatment		
Nephrectomy	2 patients	Partial nephrectomy
Transarterial embolization	3 patients	No
Palliative therapy	1 patient	No

– review and editing. Daisuke Yamada: Writing – review and editing; formal analysis. Haruki Kume: Writing – review and editing; supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The approval number for this case report is 3124.

Informed consent

Informed written consent was obtained.

Registry and the Registration No. of the study/trial

Not applicable.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request due to privacy and ethical restrictions.

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