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REVIEW ARTICLE

Recurrent Hepatocellular Carcinoma in the Right Adrenal Gland 11 Years After Liver Transplantation for Hepatocellular Carcinoma: a Case Report and Literature Review

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Abstract Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, and extrahepatic metastases are typically found during disease progression. The incidence of adrenal metastasis (AM) from HCC in autopsy series ranges from 4.6 to 12.5%, and it is the second most common site of metastasis after the lungs. To date, there have been few reports of patients who underwent adrenalectomy for isolated AM from HCC after liver transplantation (LT). A woman aged 55 years was referred to our clinic for the evaluation of a right adrenal mass that was detected by abdominal ultrasonography at another center. She had undergone liver transplantation secondary to HCC and acute liver failure due to cryptogenic liver cirrhosis 138 months previously. She had been followed up for 5 years following LT after which she declined to continue with further follow-up. After radiologic and biochemical evaluation, she underwent adrenalectomy and the histopathologic examination revealed a 10 × 8 × 7-cm adrenal mass, which was considered to be an isolated AM from HCC. To our knowledge, this is the first case of isolated AM from HCC in the literature that was diagnosed 138 months after liver transplantation. Isolated AM from HCC after LT is rare and might be detected a long time after LT. Curative surgical resection of isolated metachronous AM from HCC in the absence of disseminated disease might provide for an acceptable disease-free period after adrenalectomy.

Keywords Hepatocellular carcinoma · Liver transplantation · Adrenal metastasis

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Introduction

The most common primary malignancy of the liver is hepatocellular carcinoma (HCC), and extrahepatic metastases are typically found during disease progression [1–3]. The incidence of adrenal metastasis (AM) from HCC in autopsy series ranges from 4.6 to 12.5% [4] and it is the second most common site of metastasis following the lung [5].

Surgical resection and liver transplantation (LT) have the best outcomes and are theoretically curative treatments for patients with HCC who are operable [3, 6]. To date, there are few reports of patients with adrenalectomy for AM from HCC after LT [7–11]. In most of these reported cases, the patients developed metachronous metastasis to other sites, including the bone, lungs, kidney, and contralateral adrenal gland [8–11].

In the present report, we described a case who underwent adrenalectomy for an isolated AM from HCC 138 months after LT and reviewed the corresponding literature which

particularly included cases of AM from HCC following LT. To our knowledge, this is the first report case in the literature with isolated adrenal metastasis of HCC which was diagnosed 138 months after LT.

Case

A 55-year-old female patient has been referred to our clinic for the evaluation of a right adrenal mass that had been detected by abdominal ultrasonography (US) at another center. Her history revealed that she had undergone cholecystectomy in 1995 due to cholecystitis. During the cholecystectomy operation, the liver had been noted to have a cirrhotic appearance. She had been followed up annually for 5 years after the cholecystectomy operation with no evidence of any further abnormality related to liver cirrhosis. However, she declined follow-up at that time. Three years later, she had been re-evaluated due to some non-specific symptoms such as fatigue and weakness. Magnetic resonance imaging (MRI) has revealed a cirrhotic liver with multiple macro-nodules. In T1 and T2 sequences of MRI, a 42-mm hyper-intense mass which was located in the intersection of segments 5 and 8 has been detected and interpreted as a dysplastic nodule. Viral serology (HBsAg, anti-HBcIgG, anti-HCV, anti-HBs), autoimmune markers, and Wilson disease scan have been found to be negative. No risk factor for non-alcoholic steatohepatitis (NASH) has been noted as well. The alpha-fetoprotein (AFP) level was found to be normal, and there was no radiological evidence of metastatic disease. Acute liver failure due to cryptogenic liver cirrhosis (child B score 9) developed during the evaluation period and the patient had undergone living-donor LT. Histopathological examination of the liver revealed a 4-cm primary tumor with satellite nodules and three subcentimetric metastatic foci near the portal vein (T3bN0M0, stage IIIB). No microvascular invasion was reported. She had been followed up annually for 5 years following LT, and she received mycophenolate mofetil 500 mg/day and tacrolimus 2 mg/day during this period. No evidence of recurrence was detected with contrast-enhanced MRI and laboratory examinations during the 5-year follow-up period. Although she declined to continue further follow-up after this period, she continued to take her medications. She was admitted to the emergency room with abdominal pain 138 months after LT and a right adrenal mass was detected by US. She was referred to our clinic for further evaluation of the adrenal mass. Laboratory findings showed that the plasma levels of dehydroepiandrosterone-sulfate (DHEA-S), 17-alpha-hydroxyprogesterone, liver function tests, and AFP were all within normal ranges. The results of diagnostic hormonal tests were compatible with a non-functional adrenal mass. MRI demonstrated a heterogeneous mass with loss of signal intensity in the out-of-phase sequence in the right adrenal gland with the largest diameter measured as 10 cm (Fig. 1). Positron-emission tomography-computerized tomography (PET-CT) was performed as the large size of the adrenal mass and the history of HCC raised concern about the malignant potential of the lesion. PET-CT images revealed a right-sided uniform and homogeneous adrenal mass with mild hypermetabolic activity associated with the lesion (SUD Max: 3.6). There was no evidence of any additional mass lesions in the transplanted liver or at other sites on any of the imaging studies. The patient underwent laparotomy, and excision of the mass along with the right adrenal gland was performed. No macroscopic invasion to adjacent structures was noted during surgery. The patient had an uneventful recovery and was discharged on the postoperative seventh day under immunosuppression with tacrolimus and mycophenolate mofetil. She was followed up by MRI and laboratory evaluation at 6 months' intervals. She was still alive with no evidence of recurrent disease 36 months after surgery.

The patient was informed that we aimed to publish this case in a scientific journal, and a consent document was obtained.

Histopathologic Result

In the macroscopic examination, the tumor was yellowish white in color, measured 10 × 8 × 7 cm in size, and involved nearly the entire cut surface of the adrenalectomy specimen. On microscopic examination, a tumoral lesion with an expansive growth pattern that was sharply demarcated from the residual adrenal cortex tissue was noted (Fig. 2). The tumor cells were arranged in a pseudoglandular and trabecular pattern. They had an oxyphilic cytoplasm and round vesicular nuclei with prominent nucleoli. An immuno-histochemical evaluation showed that the tumor cells were positive for hepatocyte paraffin (HepPar-1) (Fig. 3). The adrenal mass was considered to be an isolated AM from HCC.

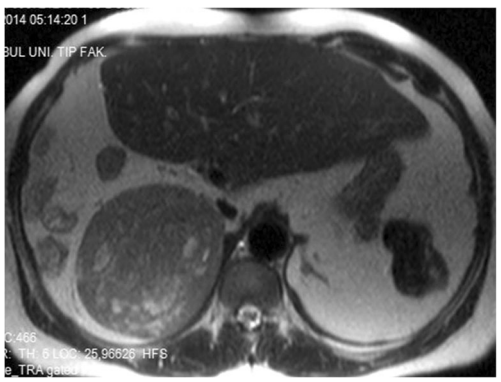

Fig. 1 Axial T2-weighted MR images show a heterogeneous 10-cm right adrenal gland mass with loss of signal intensity

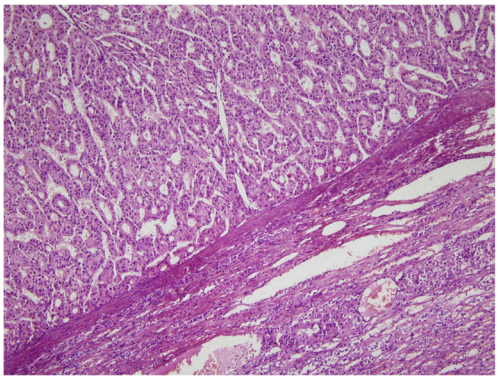

Fig. 2 Histopathologic image of adrenalectomy specimen. The tumor has a pseudoglandular and trabecular pattern and is demarcated from adrenal cortex tissue (a) (H&E, ×10)

Discussion

After liver resection for the primary tumor, recurrence is mostly seen in the remnant liver and is the main cause of disease-related mortality [12]. The most common sites of extrahepatic metastasis of HCC are the lungs, abdominal lymph nodes, bones, and adrenal glands [13, 14]. Isolated metachronous AM from HCC after an initial surgery is rare. A review of the relevant English-language medical literature identified only 11 case reports (4 case reports and 1 series including 7 patients), which described the treatment and outcomes of particular patients with isolated metachronous AM from HCC after LT [7–11] (Table 1). The largest diameters of isolated adrenal metastatic lesions were reported to range between 27 and 44 mm [7, 9]. The median time between LT and recurrence of HCC was found as 12.3 months (range, 1.5–60.3 months) [15]. To our knowledge, this is the first case in the literature with such a long interval between LT (138 months) and the detection of an isolated large metachronous AM. In the present case report, the largest diameter of the AM was measured as 10 cm which was larger than that of the reported cases in the literature. Popescu et al. reported the rate of metachronous AM from HCC as 0.5% in 174 patients after liver resection [16]. Ha et al. documented that the rates of metachronous AM from HCC after liver resection or LT were 0.5 and 0.6%, respectively, in a total of 5356 patients [8]. The clinical course of the patients with HCC has been evaluated previously in two studies which were conducted at the Gastroenterology Department of our clinic [17, 18]. In these two studies, the rate of extrahepatic metastasis ranged between 4.8 and 11% [17, 18]. None of the patients in these studies had isolated AM [16, 17]. Ha et al. analyzed the outcomes of seven patients who underwent adrenalectomy for metachronous AM from HCC after liver resection or LT [8]. In their study, the interval period between LT and adrenalectomy ranged from 21 to 58 months. The authors reported that four of these seven patients developed further recurrences following adrenalectomy at other sites and the 5-year survival rate after adrenalectomy was 85.7% [8]. Isolated left AM from HCC was reported 6 months after LT in a publication from Spain [9]. The patient underwent left adrenalectomy, but developed an isolated right AM 8 months after left adrenalectomy and a right adrenalectomy was performed. The authors reported that the patient was still free of recurrent disease 4 years after LT. Chen et al. reported a patient who underwent two surgical operations due to metachronous lung and adrenal metastasis from HCC and was still disease-free 3 years after the surgical procedures [10]. Choi et al. documented a 71-year-old male patient who was treated with left adrenalectomy due to AM from HCC which was detected 11 months after LT [11]. This patient developed multiple intrahepatic recurrent nodules 2 months after adrenalectomy and died of liver failure 16 months after surgery. Rubio et al. reported a case of isolated AM from HCC that was detected 3 years after LT and was treated by transabdominal adrenalectomy [7].

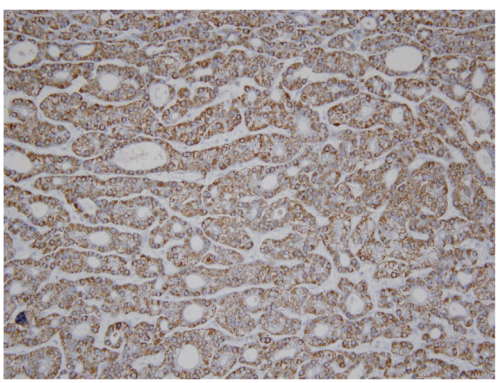

Fig. 3 Immuno-histochemical staining image. Positive staining of tumor cells with HepPar-1 (b) (×20)

During the follow-up after LT or liver resection for HCC, diagnostic examinations should include MRI or CT and serum AFP assays. AFP assays during follow-up are more important in patients who initially present with elevated AFP levels. Twice-yearly screening of patients is recommended after LT. Annual follow-up has resulted in poorer outcome than twice-yearly follow-ups [3]. Increased baseline AFP level is a strong predictor of vascular invasion and survival in patients with HCC [17]. In patients with isolated metachronous AM from HCC after LT, adrenalectomy was suggested to improve outcomes and survival, particularly in patients with preserved liver function, no evidence of metastatic disease at other sites, and in good general condition [8]. In patients with suspected AM from HCC after LT, PET scans or CT imaging is helpful to exclude metastatic disease in the liver or at other sites prior to adrenalectomy [8]. Surgical resection of isolated AM from HCC can be accomplished through laparotomy, laparoscopic, or retroperitoneal approaches. In our patient, we performed a PET scan additional to CT and MRI to investigate the fluorodeoxyglucose (FDG) avidity of the adrenal mass and to evaluate the presence of systemic metastatic disease. We preferred to perform adrenalectomy via laparotomy in our

Table 1 Literature review of patients who underwent adrenalectomy for metachronous isolated adrenal metastasis after liver transplantation

Authors	Rubio et al. [7]	Ha et al. [8]	Castroagudin et al. [9]	Chen et al. [10]	Choi et al. [11]
No. of pts	1	7	1	1	1
Age (yrs)/sex	23 / male	56.1 ± 10.2 / Male	51 / male	60 / male	71 / male
Size (mm)	27	34 ± 18 (mean)	44	35	35
Location of metastasis	Right adrenal	Right adrenal (n = 4) Left adrenal (n = 3)	Left adrenal	Right lung	Left adrenal
Time after LT (mo)	36	21–58	6	33	11
Imaging prior to surgery	CT	PET scan & MRI	CT	PET scan	CT
Type of surgery	Right adrenalectomy	Adrenalectomy Open (n = 6) Laparoscopic (n = 1)	Left adrenalectomy	Partial right lung resection	Retroperitoneal left adrenalectomy
Further recurrence	Not mentioned	Pulmonary, renal, intrahepatic, peritoneal, bone (n = 4)	Right adrenal gland	Left AM of 40 mm detected 6 months after lung resection	Intrahepatic recurrence 2 mo after adrenalectomy
Surgery for further recurrence	Not mentioned	Pulmonary metastasectomy, nephrectomy	Right adrenalectomy	Laparoscopic left adrenalectomy	-
Additional treatment	Not mentioned	Chemotherapy	Not mentioned	Chemotherapy	Chemotherapy, TACE*
Outcome after adrenalectomy	Not mentioned	5-year survival rate 85.7%	Still alive after 48 mo	Still alive after 36 mo	Expired 16 mo after adrenalectomy

*TACE: Transarterial chemoembolization

patient. Non-operative procedures such as transarterial embolization, percutaneous ethanol injection, radiotherapy, or systemic chemotherapy are recommended in patients with metachronous AM who are not suitable for surgery due to poor liver function, poor general condition, or systemic metastatic disease [19].

In conclusion, isolated AM from HCC after LT is rare and might be detected after a long period of time following LT. Imaging studies including CT, MRI, and PET are helpful to evaluate the presence of other intrahepatic or extrahepatic metastatic foci in patients with suspected AM from HCC. Curative surgical resection of isolated metachronous AM from HCC in the absence of disseminated disease might provide for acceptable disease-free survival periods after adrenalectomy.

AM, adrenal metastasis; CT, computerized tomography; HCC, hepatocellular carcinoma; HepPar-1, hepatocyte paraffin; LT, liver transplantation; MRI, magnetic resonance imaging; PET-CT, positron-emission tomography-computerized tomography; TACE, transarterial chemoembolization

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Compliance with Ethical Standards The patient was informed that we aimed to publish this case in a scientific journal, and a consent document was obtained.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Maki A, Takayatsu T, Mori K, Shimahara Y, Yamaoka Y, Ozawa K (1989) Studies on multidisciplinary therapy for recurrent hepatocellular carcinoma after hepatic resection. Jpn J Gastroenterol Surg 22: 779–782. doi:https://doi.org/10.5833/jjgs.22.779
2. Hsieh MH, Lin ZY, Chuang WL, Huang CJ, Shih MC (2005) Management of bilateral adrenal metastases from hepatocellular carcinoma: a case report. Kaohsiung J Med Sci 21(8):371–376. doi:https://doi.org/10.1016/S1607-551X(09)70136-6
3. Forner A, Llovet JM, Bruix J (2012) Hepatocellular carcinoma. Lancet 379:1245–1255. doi:https://doi.org/10.1016/S0140-6736(11)61347-0
4. Kitaoka F, Yanaga K, Okudaira S, Tajima Y, Furui J, Kanematsu T (2005) Successful left adrenalectomy for metastatic hepatocellular carcinoma using hand-assisted laparoscopic surgery: report of a case. Surg Today 35(2):172–174. doi:https://doi.org/10.1007/s00595-004-2891-5
5. Nakashima T, Okuda K, Kojiro M et al (1983) Pathology of hepatocellular carcinoma in Japan: 232 consecutive cases autopsied in ten years. Cancer 51:863–877. doi:https://doi.org/10.1002/1097-0142(19830301)51:5<863
6. Kooby DA, Jarnagin WR (2004) Surgical management of hepatic malignancy. Cancer Investig 22(2):283–303. doi:https://doi.org/10.1081/ CNV-120030217

7. Rubio E, González J, Jimenéz M et al (2009) Right adrenal metastases of hepatocarcinoma after liver transplantation: case report and literature review. Transplant Proc 41:1067–1069
8. Ha TY, Hwang S, Ahn CS et al (2015) Resection of metachronous adrenal metastasis after liver resection and transplantation for hepatocellular carcinoma. Dig Surg 31(6):428–435. doi:https://doi.org/10.1159/000370078
9. Castroagudín JF, Gonzalez-Quintela A, Martinez J, Tomé S, Forteza J, Varo E (2001) Bilateral adrenal metastases from hepatocellular carcinoma after liver transplantation. Hepato-Gastroenterology 49(43):249–251
10. Chen SW, Wang S, Wang B, Li WD, Yan S, Xie LP (2011) Metachronous pulmonary and adrenal metastases after liver transplantation for hepatocarcinoma. World Journal of Surgical Oncology 9(1):1. doi:https://doi.org/10.1186/1477-7819-9-156
11. Choi SB, Kim H, Kim SH, Park YN, Kim KS (2011) Solitary extrahepatic intraabdominal metastasis from hepatocellular carcinoma after liver transplantation. Yonsei Med J 52:199–203. doi:https://doi.org/10.3349/ymj.2011.52.1.199
12. McLean K, Lilienfeld H, Caracciolo JT, Hoffe S, Tourtelot JB, Carter WB (2011) Management of isolated adrenal lesions in cancer patients. Cancer Control 18(2):113–126
13. Chua TC, Morris DL (2012) Exploring the role of resection of extrahepatic metastases from hepatocellular carcinoma. Surg Oncol 21:95–101. doi:https://doi.org/10.1016/j.suronc.2011.01.005
14. Uchino K, Tateishi R, Shiina S et al (2011) Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. Cancer 117:4475–4483. doi:https://doi.org/10.1002/cncr.25960
15. Roayaie S, Schwartz JD, Sung MW et al (2004) Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. Liver Transpl 10(4):534–540. doi:https://doi.org/10.1002/lt.20128
16. Popescu I, Alexandrescu S, Ciurea S et al (2007) Adrenalectomy for metastases from hepatocellular carcinoma—a single center experience. Langenbeck's Arch Surg 392(3):381–384. doi:https://doi.org/10.1007/s00423-006-0135-4
17. Ekinci O, Baran B, Ormeci AC et al (2015) Baseline alfa-fetoprotein level is a strong predictor of vascular invasion and survival in patients with hepatocellular carcinoma. Hepatology 58:1251A–1251A
18. Akyuz F, Evirgen S, İliaz R et al (2016) Clinical yield of radioembolization in hepatocellular carcinoma? Hepatol Int 10(Suppl 1):S325
19. Uenishi T, Yamazaki O, Matsuyama M, Horjii K, Yamamoto T, Kubo S (2005) Surgical management of bilateral adrenal metastases from hepatocellular carcinoma after transcatheter arterial embolization. Osaka City Med J 51(2):89–93