Fifteen-year-long journey with hepatocellular carcinoma from diagnosis during pregnancy to recurrence after liver transplantation: A case report of intractable tumor recurrence

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Received June 1, 2021
Revised June 25, 2021
Accepted June 29, 2021
Published online July 14, 2021

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Hepatocellular carcinoma (HCC) during pregnancy is very rare and reported to be associated with inferior prognosis. We herein present a case of a patient who was diagnosed with HCC at the age of 26 years during pregnancy. The patient was infected with hepatitis B virus through vertical transmission. After full-term vaginal delivery, the patient underwent transarterial chemoembolization (TACE) twice and right hepatectomy consecutively. One year later, TACE was repeated and second hepatectomy was performed. Four years later, TACE was repeated and third hepatectomy was performed. Two years later, TACE was repeated and fourth hepatectomy was performed. Two years later, HCC recurred around the left hepatic duct and external beam radiotherapy was performed. Subsequently, biliary stenosis occurred, thus endoscopic retrograde biliary drainage tube was inserted. One year later, her liver function deteriorated with tumor progression and portal vein occlusion. The patient underwent deceased donor liver transplantation using an HBsAg-positive whole liver graft. At posttransplant 6 months, pulmonary metastasis occurred, which was managed with pulmonary metastasectomy twice and radiotherapy. The patient passed away 20 months after transplantation because of HCC progression. The patient had suffered from HCC for 15 years, in which she underwent hepatectomy four times, TACE 10 times, liver transplantation, pulmonary metastasectomy twice, and radiotherapy three times. The patient demonstrated unusual long-term intractable course of HCC recurrence refractory to various locoregional treatments.

Keywords: Pregnancy; Locoregional treatment; Repeat hepatectomy; Liver transplantation; Metastasectomy

INTRODUCTION

Hepatocellular carcinoma (HCC) during pregnancy is very rare, although HCC is the most frequent primary tumor

in the liver and the fifth most common cancer worldwide [1,2]. There is controversy regarding whether HCC during pregnancy is different from HCC seen in non-pregnant women. Some studies reported more aggressive behav-

ior of HCC during pregnancy, and some have suggested that this results from the elevated levels of sex hormones [3]. Treatment of HCC is difficult because tumors recur frequently after various locoregional treatments. Repeated re-resection has also been done in a few patients with local tumor recurrence [4,5]. We herein present a case of a patient who suffered from intractable HCC recurrence for 15 years, from initial diagnosis of HCC during pregnancy to patient death because of posttransplant recurrence.

CASE PRESENTATION

The case was a female patient who had been diagnosed with HCC at the age of 26 years when she was in the late third trimester of pregnancy. She had hepatitis B virus (HBV) infection through vertical transmission from her mother. Elevation of liver enzyme levels led to performance of abdominal ultrasonography, by which a 1.5-cm-sized HCC was detected. At 2 months after full-term vaginal delivery, she underwent transarterial chemoembolization (TACE) twice (Fig. 1). However, HCC was not effectively treated, thus right hepatectomy was performed.

At 1 year later, local tumor recurrence occurred at the remnant segment IV resulted, so TACE was performed twice, but it was also ineffective. Partial hepatectomy of the segment IV was performed to remove the recurrent HCC lesions (Fig. 2) [6].

Four years after the second hepatectomy, HCC recurred at the remnant paracaval portion of the caudate lobe. This recurrent mass also did not respond to repeated TACE, so she underwent isolated caudate lobectomy. Soon after that, she underwent re-exploration due to iatrogenic bowel injury. By the age of 33 years, she had undergone three liver resections and one bowel surgery.

At two years after the third hepatectomy, at the age of

35 years, the patient visited our institution for treatment of the two recurrent HCC lesions at the remnant segments IV and III. TACE was repeated twice, but viable portions still remained (Fig. 3). We decided to perform the fourth liver resection. After laparotomy, time-consuming meticulous dissection of the whole right subphrenic fossa led to sufficient exposure of the remnant liver. The remnant segment IV and some of the segment III parenchyma including the recurrent HCC were meticulously resected (Fig. 4) [7]. The patient recovered uneventfully and underwent prophylactic adjuvant external beam radiotherapy in the liver transection area because three repeat resections had been done at that site.

Two years later, at the age of 37 years, HCC recurred around the left hepatic duct, so external beam radiotherapy was performed. Subsequently, biliary stenosis occurred, thus endoscopic retrograde biliary drainage tube was in-

Fig. 1. Computed tomography finding of the hepatocellular carcinoma after the initial two sessions of transarterial chemoembolization.

Fig. 2. Intraoperative finding of the second hepatectomy. (A) Two masses (circles) are visible before partial hepatectomy of segment IV. (B) The recurrent masses are visible at the resected liver specimen.

Fig. 3. Sequences of treatment with transarterial chemoembolization after the third hepatectomy. Two recurrent masses (A) were treated with transarterial chemoembolization twice (B, C), resulting in control of the recurrent masses (D).

Fig. 4. Perioperative finding of the fourth hepatectomy. (A, B) The remnant segment IV and some of segment III parenchyma including the recurrent mass were resected. (C, D) Intraoperative cholangiography is taken to check the anatomy of the remnant left hepatic duct using a segment III bile duct branch.

serted (Fig. 5).

At the age of 38 years, a follow-up computed tomography scan revealed progression of the recurrent HCC with complete occlusion of the portal vein (Fig. 6). Her general

condition deteriorated rapidly, so she was enrolled on the waiting list for deceased donor liver transplantation (LT). The patient had no potential living donors because most of her family members were hepatitis B surface antigen (HB-

sAg)-positive. After 1 month's waiting, a marginal liver graft of an HBsAg-positive deceased donor was allocated.

During recipient hepatectomy, the abdomen was heavily adhered because of the previous four hepatectomies and one bowel surgery. The suprahepatic inferior vena cava (IVC) was heavily adhered to the diaphragm, so extensive dissection for clamping of the IVC at the diaphragm level was not possible. Inevitably, graft outflow vein reconstruction using a double IVC reconstruction technique was performed after dissection of the retrohepatic IVC. Other reconstruction procedures were similar to the standard procedures of whole liver graft implantation.

The explant liver showed a 1-cm-sized recurrent HCC at the soft tissue of the hepatic hilum with perineural invasion. Another HCC was also located in the bile duct. Metastatic HCC was identified at 2 of the 2 lymph nodes. No tumor cells were found at the portal vein thrombus (Fig. 7).

Early follow-up computed tomography showed extrinsic compression-associated stenosis of the IVC reconstruction, so IVC wall stenting was performed to resolve the graft outflow vein obstruction (Fig. 8).

Fig. 5. Endoscopic management of the radiation therapy-induced bile duct stenosis. (A) Biliary stenosis is identified on endoscopic retrograde cholangiography. (B) An endoscopic retrograde biliary drainage tube is inserted.

Fig. 6. Computed tomography taken after internal biliary drainage. (A) Recurrent mass occurred around the left hepatic duct. (B) The left portal vein is completely occluded (arrow).

After LT, the patient was continuously HBsAg-positive despite active HBV treatment with high-dose hepatitis B immunoglobulin and lamivudine. At 6 months after LT, solitary pulmonary metastasis was found at the right lower lung, which was resected. Soon after the pulmonary metastasectomy, multiple lung metastasis occurred. At 3 months after the first pulmonary metastasectomy, five metastatic masses were also resected at the right and left lungs (Fig. 9). At 3 months after the second pulmonary metastasectomy, multiple lung metastasis occurred again, so external beam radiation therapy was performed. After 3 months, multiple HCC recurrence occurred in the abdomen, showing progression of intraductal bile duct metastasis, metastatic lymphadenopathy in the gastrohepatic ligament and perihepatic space, and pleural metastasis with left pleural effusion. The patient passed away 20 months after LT be-

Fig. 7. Gross photograph of the explant liver showing overt liver cirrhosis and cholestasis.

Fig. 8. Sequences of treatment for graft outflow vein stenosis. (A, B) Early posttransplant computed tomography shows focal stenosis (arrow) at the suprahepatic inferior vena cava area, which was dilated by a wall stent. (C, D) A wall stent is inserted to relieve the stenosis (arrow) at the inferior vena cava.

Fig. 9. Sequences of treatment for lung metastasis. (A) Multiple lung metastases are identified. (B) A resected lung specimen is visible after the second pulmonary metastasectomy. (C) Fluorodeoxyglucose positron emission tomography shows multiple lung metastases. (D) External beam radiotherapy is planned with simulation.

cause of HCC progression. The patient had suffered from HCC for 15 years, in which she underwent hepatectomy four times, TACE 10 times, deceased donor LT, pulmonary metastasectomy twice, and radiotherapy three times.

DISCUSSION

HCC is the most frequent primary tumor in the liver and the fifth most common cancer worldwide [2]. The incidence of HCC is especially high in some parts of Asia and Africa, but has also increased over the past decade in the United States and northern Europe [8,9]. This epidemiologic change has probably resulted from increased immigration, especially from Asia [2]. Although the worldwide incidence of HCC in women is 5.5 of 10,000 [2], HCC during pregnancy is so rare that less than 50 cases have been reported worldwide [1].

It is important to consider both the mother and the fetus when treating pregnant patients with HCC. Pregnancy also presents an obstacle for diagnosing and treating HCC. These factors add to the complexity of diagnostic and therapeutic plans. There is controversy over whether the HCC during pregnancy is different from the HCC seen in non-pregnant women. Many authors have reported more aggressive behavior of HCC during pregnancy and some have suggested that this results from the elevated levels of sex hormones [3,9-13], suggesting that pregnancy was an adverse factor for the prognosis of HCC. Several theories have been proposed on how estrogen affects the development of HCC such as through accelerated mitosis of hepatocytes, development of hypervascularity, production of hydroxyl free radicals associated with mutation, decreased humoral immunity leading to susceptibility to tumorigenesis, and reactivation of HBV [14-17]. However, there is no supporting biological evidence for these theories. Several trials of tamoxifen treatment for HCC had disappointing outcomes [16].

The mean number of gestational weeks at the time of HCC diagnosis during pregnancy was 24.1 ± 8.4 [1]. The choice between continuing and terminating the pregnancy presents a difficult problem for both the patient and physician. In cases that are diagnosed early, termination of the pregnancy may be the more appropriate choice, whereas in cases diagnosed late, beginning therapy after induced delivery or cesarian section may be preferable.

Our present patient underwent hepatectomy for HCC four times before LT. Such repetition of hepatectomy is rare and unique [4,5], because the tumor was not responsive

to TACE and radiotherapy and the location of recurrent tumors were not suitable for radiofrequency ablation.

After repetition of various locoregional treatments, the tumor finally invaded the bile duct and the portal vein was also occluded. The patient suffered from HCC progression, obstructive jaundice and hepatic failure. Since these clinical features exceeded the eligible criteria for LT, the patient was not indicated for priority allocation of deceased donor LT. Macroscopic bile duct tumor thrombosis is a significant risk factor for posttransplant HCC recurrence, as is portal vein tumor thrombosis [18,19].

While waiting for deceased donor LT, we decided to use a marginal HBsAg-positive liver graft, because there was no other way for her to receive LT, and we had experienced favorable outcomes after LT with HBsAg-positive liver grafts [20,21]. Because of heavy adhesion from her five prior abdominal operations, recipient hepatectomy was very difficult and time-consuming. Because the suprahepatic IVC was heavily adhered to the diaphragm, thus dissection for clamping of the IVC at the diaphragm level was not possible. Double IVC reconstruction under incomplete isolation of the recipient IVC resulted in extrinsic compression-associated stenosis of the IVC reconstruction, which was resolved by endovascular stenting. Such treatment with IVC stenting has been occasionally performed to LT recipients with graft-associated extrinsic compression of the IVC [22].

After her recovery from the LT operation, management of HBV infection was demanding because graft liver function fluctuated despite combination therapy with hepatitis B immunoglobulin and an antiviral agent. It was suggested that hepatitis B immunoglobulin should be abandoned in recipients of HBsAg positive liver grafts, in whom HBV prophylaxis could be done with only oral antiviral therapy [23].

Because HCC was far advanced at the time of LT, HCC recurred early in the lung and progressed rapidly at the lungs and abdomen. The patient suffered from HCC recurrence for 15 years and the HCC treatment included hepatectomy four times, TACE 10 times, deceased donor LT, pulmonary metastasectomy twice, and radiotherapy three times.

There is no reliable information showing that the tumor biology of HCC in this patient was more aggressive than that in other patients, from the current viewpoint of HCC development during pregnancy. However, her HCC was resistant to TACE and radiotherapy and prone to induce local recurrence after repeated hepatic resection. The patient demonstrated unusual long-term intractable course of HCC recurrence refractory to various locoregional treatments.

FUNDING

There was no funding related to this study.

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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AUTHORS' CONTRIBUTIONS

Conceptualization: SH. Data curation: DHJ. Methodology: SH, DHJ, TYH. Visualization: SH. Writing - original draft: SH. Writing - review & editing: All.

REFERENCES

- Choi KK, Hong YJ, Choi SB, Park YN, Choi JS, Lee WJ, et al. Hepatocellular carcinoma during pregnancy: is hepatocellular carcinoma more aggressive in pregnant patients? *J Hepatobiliary Pancreat Sci* 2011;18:422-431.
- Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;362:1907-1917.
- Lau WY, Leung WT, Ho S, Lam SK, Li CY, Johnson PJ, et al. Hepatocellular carcinoma during pregnancy and its comparison with other pregnancy-associated malignancies. *Cancer* 1995;75:2669-2676.
- Liu J, Zhao J, Gu HAO, Zhu Z. Repeat hepatic resection VS radiofrequency ablation for the treatment of recurrent hepatocellular carcinoma: an updated meta-analysis. *Minim Invasive Ther Allied Technol* <https://doi.org/10.1080/13645706.2020.1839775> [Epub ahead of print].
- Nakajima Y, Ko S, Kanamura T, Nagao M, Kanehiro H, Hisanaga M, et al. Repeat liver resection for hepatocellular carcinoma. *J Am Coll Surg* 2001;192:339-344.
- Choi KK, Hong YJ, Choi SB, Yi NJ, Hwang S, Park YN, et al. A case of hepatocellular carcinoma in a pregnant patient in twenties. *J Liver Cancer* 2009;9:76-81.
- Hwang S, Choi BH, Song GW, Park GC, Park YH, Moon DB, et al. Technique of antegrade intraoperative cholangiography not requiring hepatic hilar dissection during repeated hepatectomy for hepatocellular carcinoma. *Hepatogastroenterology* 2012;59:878-880.
- El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med* 2003;139:817-823.
- Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004;127(5 Suppl 1):S5-S16.
- Cobey FC, Salem RR. A review of liver masses in pregnancy and a proposed algorithm for their diagnosis and management. *Am J Surg* 2004;187:181-191.
- Jeng LB, Lee WC, Wang CC, Chen MF, Hsieh TT. Hepatocellular carcinoma in a pregnant woman detected by routine screening of maternal alpha-fetoprotein. *Am J Obstet Gynecol* 1995;172(1 Pt 1):219-220.
- Gisi P, Floyd R. Hepatocellular carcinoma in pregnancy. A case report. *J Reprod Med* 1999;44:65-67.
- Alvarez de la Rosa M, Nicolás-Pérez D, Muñiz-Montes JR, Trujillo-Carrillo JL. Evolution and management of a hepatocellular carcinoma during pregnancy. *J Obstet Gynaecol Res* 2006;32:437-439.
- Goldberg I, Hod M, Katz I, Friedman S, Ovadia J. A case of hepatocellular carcinoma in pregnancy detected by routine screening of maternal alpha-feto-protein. *Acta Obstet Gynecol Scand* 1991;70:241-242.
- Hsieh TT, Hou HC, Hsu JJ, Hsieh CC, Jeng LB. Term delivery after hepatocellular carcinoma resection in previous pregnancy. *Acta Obstet Gynecol Scand* 1996;75:77-78.
- De Maria N, Manno M, Villa E. Sex hormones and liver cancer. *Mol Cell Endocrinol* 2002;193:59-63.
- Stanford JL, Thomas DB. Reproductive factors in the etiology of hepatocellular carcinoma. The WHO collaborative study of neoplasia and steroid contraceptives. *Cancer Causes Control* 1992;3:37-42.
- Ha TY, Hwang S, Moon DB, Ahn CS, Kim KH, Song GW, et al. Long-term survival analysis of liver transplantation for hepatocellular carcinoma with bile duct tumor thrombus. *Transplant Proc* 2014;46:774-777.
- Kim JM, Kwon CH, Joh JW, Park JB, Gwak MS, Lee JH, et al. The effect of hepatocellular carcinoma bile duct tumor thrombi in liver transplantation. *Hepatogastroenterology* 2014;61:1673-1676.
- Hwang S, Lee SG, Park KM, Kim KH, Ahn CS, Oh HB, et al. Five-year follow-up of a hepatitis B virus-positive recipient of hepatitis B surface antigen-positive living donor liver graft. *Liver Transpl* 2006;12:993-997.
- Namgoong JM, Hwang S, Kim DY, Ha TY, Song GW, Jung DH, et al. Pediatric liver transplantation using a hepatitis B surface antigen-positive donor liver graft for congenital absence

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- of the portal vein. Korean J Transplant 2021;35:59-65.
22. Lee S, Park K, Hwang S, Kim K, Ahn C, Moon D, et al. Anterior segment congestion of a right liver lobe graft in living-donor liver transplantation and strategy to prevent congestion. J Hepatobiliary Pancreat Surg 2003;10:16-25.
 23. Yu S, Yu J, Zhang W, Cheng L, Ye Y, Geng L, et al. Safe use of liver grafts from hepatitis B surface antigen positive donors in liver transplantation. J Hepatol 2014;61:809-815.