Case Report

Liver Transplantation for Hepatic Adenomatosis: The First Case Report in Thailand and Literature Review

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Hepatic adenomas are benign solid liver tumors commonly found in young females and usually asymptomatic. Hepatic adenomatosis is characterized by more than 10 adenomas in an otherwise normal liver. Bleeding and malignant transformation uncommonly occur especially in tumor larger than 5 cm and in male patients. The authors reported a case of a young female with large multiple hepatic adenomas from hepatic adenomatosis that presented with abdominal pain, large abdominal mass, weight lost, and abnormal liver function tests. She failed transarterial embolization. Surgical resection was not offered due to extent of the hepatic adenomas. She received orthotopic liver transplantation as rescue therapy. Her explanted liver showed multiple foci of hepatocellular carcinoma (HCC). Her post-operative was uneventful. The authors reported a case of liver transplantation for the treatment of unresectable hepatic adenomatosis.

Keywords: Hepatic adenomatosis, Malignant transformation, Liver transplantation

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Hepatic adenomas are benign solid liver tumors often found in young females. Hepatic adenomatosis consists of 10 or more hepatic adenomas in a normal liver in the absence of glycogen storage disease or vascular disease(1). Hepatic adenomatosis is present in 10% to 24% of patients with hepatic adenoma(2). The presentation of hepatic adenomas ranges from asymptomatic, abdominal pain or bloating, and hemorrhage to malignant transformation. The two most common managements for hepatic adenoma are surveillance and resection. The common indications for resection are symptomatic or large at more than 5 cm. Liver transplantation can be used as a rescue therapy for patients with multiple large unresectable hepatic adenomas. The authors reported a case of a female patient that underwent successful liver transplantation for treatment of her hepatic adenomatosis.

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Case Report

A 43-years-old Thai female came to the author's clinic for a second opinion for her liver mass. Two months prior, she had gone to see her physician with complaint of abdominal pain and fullness. A large palpable mass was found in her right upper quadrant of her abdomen. She was referred to another hospital for further investigation. Her abdominal computed tomography (CT) revealed multiple heterogeneous enhancing masses with some internal fat component in both hepatic lobes. The large liver nodules were biopsied and showed consistent with hepatic adenoma. She underwent transarterial chemoembolization after suspicion for the diagnosis of hepatocellular carcinoma (HCC). She came to see the authors for a second opinion to treat her liver masses in September 2019.

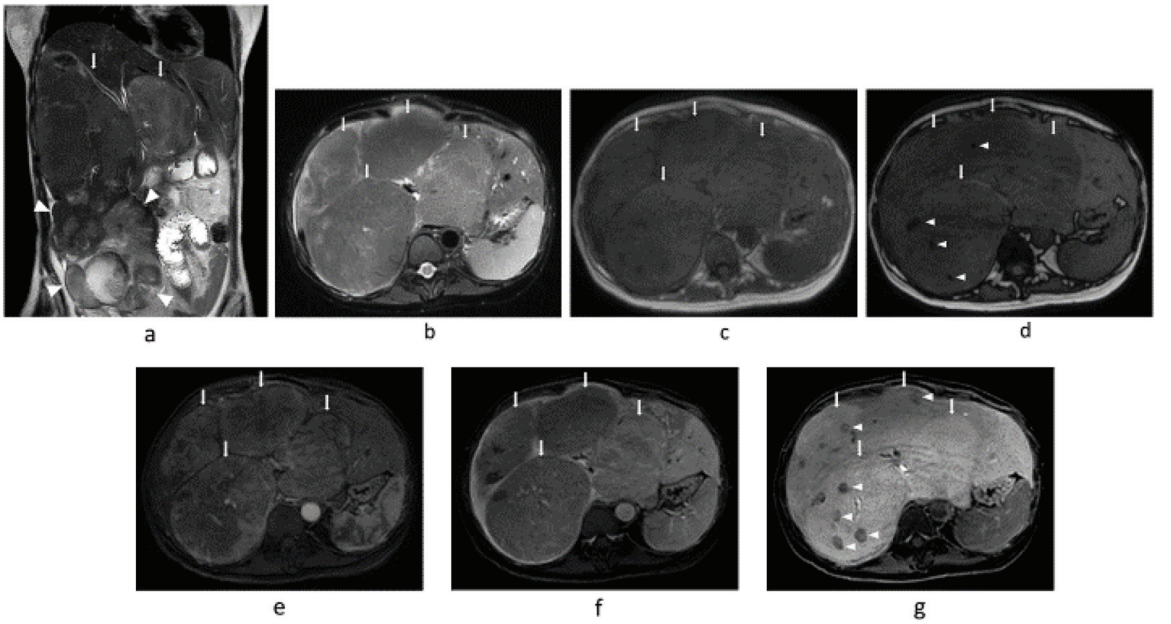

Figure 1. Coronal T2-weighted (a) and axial T2-weighted (b) MR images depicted multiple well-defined mildly T2 hyperintense lesions (arrows in a and b) with a large exophytic lesion arising from hepatic segment V (arrow heads in a). The lesions contained significant amount of fat as demonstrated by isointense to the liver on the T1-weighted in-phase image (arrows in c) with areas of signal drop-off on the out-of-phase image (arrows in d) and several small fat foci in some lesions (arrow heads in d). Axial T1-weighted contrast-enhanced MR images obtained in the arterial (e), portal venous (f) and hepatobiliary (g) phases showed heterogeneous arterial enhancement in the arterial phase (arrows in e), washout in the portal ve¬nous phase (arrows in f) and slightly hyperintense in hepatobiliary phase (arrows in g) with internal several hypointense foci (arrow heads in g).

Her physical examination revealed mild pale conjunctiva and mild jaundice. Chest examination revealed decreased breath sound at right lung base. Cardiovascular examination was unremarkable. Her abdominal examination revealed scaphoid abdomen with bulging abdominal mass on her right upper quadrant extending from the liver to the level of her umbilicus. The mass was lobulated with firm consistency extending from right costal margin to her right lower quadrant. There were no stigmata of chronic liver diseases. Extremities showed no peripheral edema.

The laboratory investigation revealed Hb 11.1 g/dL, white blood cell (WBC) 9,200 cells/mm^3, platelet 795,000 cell/mm^3. Serum aspartate aminotransferase 110 U/L (normal range 5 to 34 U/L), serum alanine aminotransferase 10 U/L (normal range 0 to 55 U/L), alkaline phosphatase 335 U/L (normal range 40 to 150 U/L), direct/total bilirubin 2.0/3.4 mg/dL (normal range <0.5/1.2 mg/dL), albumin 33 (normal range 35 to 50 g/dL), alpha-fetoprotein (AFP) 1,972 ng/mL (normal range 0 to 7.0 ng/mL), international normalized ration (INR) 1.21 and creatinine 0.22 mg/dL.

Her blood test revealed HBsAg negative, anti-HBc negative and anti-HBs positive. The anti-HCV and anti-HIV were negative. Her genetic testing revealed heterozygous PMS2 mutation, c.2380C>T.

Magnetic resonance imaging (MRI) abdomen revealed hepatomegaly with multiple well-defined mildly T2 hyperintense lesions in both hepatic lobes with large exophytic lesion arising from hepatic segment 5 extending into right-sided pelvic cavity, measuring 16.3×12.5 cm in size. The lesion contained significant amount of fat with area of signal drop-off on the out-of-phase image and several small fat foci in some lesions. Axial T1-weight contrast-enhanced MRI showed heterogenous arterial enhancement in arterial phase, wash out in portal phase and slightly hyperintense on hepatobiliary phase with internal several hypointense foci (Figure 1).

A liver mass was biopsied again at the authors' institution and showed borderline hepatocellular neoplasm with focal loss of reticulin framework and diffusely homogenous expression of glutamine synthetase immunohistochemistry, indicating a strong correlation with β-catenin activation. The histologic findings were insufficient for an unequivocal diagnosis of HCC. The atypical hepatocellular adenoma was diagnosed (Figure 2).

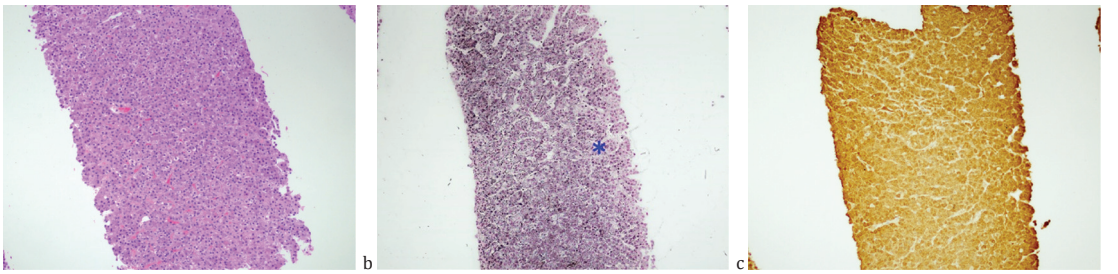

Figure 2. The biopsy of the largest mass revealed one-to-two cell thick hepatic cords. No small cell change was identified (HE, 40x) (a), focal loss of reticulin framework (*) within the lesion (reticulin, 40x) (b), diffusely positive for glutamine synthetase (glutamine synthetase, 40x) (c).

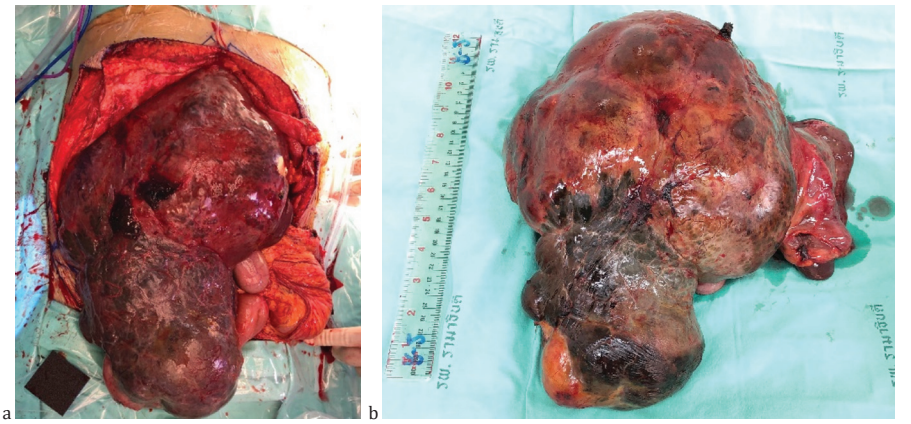

Figure 3. Intraoperative view of the liver with multiple hepatic adenoma (a) and the entire liver after being removed (b).

Her bone scan was done as a liver tumor screening protocol for liver transplantation in the authors' institution and the result was unremarkable.

She was put on the waiting list for liver transplantation after completion of the assessment process. She underwent cadaveric liver transplantation in January 2020.

The bilateral subcostal incision with midline extension was made. She was found to have multiple large liver masses in both lobes of the liver, the entire liver weight was 5.9 kg. There were some difficulties to identified all the major blood vessels including portal vein and hepatic artery due to effect of the large liver masses. The common bile duct, hepatic arteries, portal vein, supra- and infrahepatic inferior vena cava (IVC) were identified and the liver was dissected from the sub diaphragmatic region. The deceased donor liver transplantation was done with end-to-end IVC anastomosis, end-to-end anastomosis of portal vein, hepatic artery, and bile duct. The anastomoses of hepatic artery and portal vein were carried out with some difficulties due to the distorted anatomy. The transplant surgery team foreseen some of the obstacles from the patient imaging prior to the operation. The estimated blood loss was 5,000 ml (Figure 3).

Pathology from her explant liver showed multiple hepatocellular lesions (more than 20) in various sizes and stages, included hepatocellular adenomas, atypical hepatocellular adenomas (up to 14 cm, focal loss of reticulin framework) and multiple small (0.4 to 1.5 cm) foci of well-differentiated HCC (loss of reticulin framework). Tumors were confined to the liver with small vessel invasion. The gallbladder showed chronic cholecystitis (Figure 4-6).

She received corticosteroid, mycophenolate mofetil, and tacrolimus for her immunosuppression. Her postoperative course was uneventful, and she was discharged from hospital three weeks after her liver transplantation. She remained well after six months post liver transplantation. The CT scan of her abdomen showed normal size liver with no enhancing mass and patent all anastomoses. Her AFP level returned to normal range at six months post liver transplantation. The liver imaging will be done every six months according to the authors' protocol to follow-up after liver transplantation for HCC.

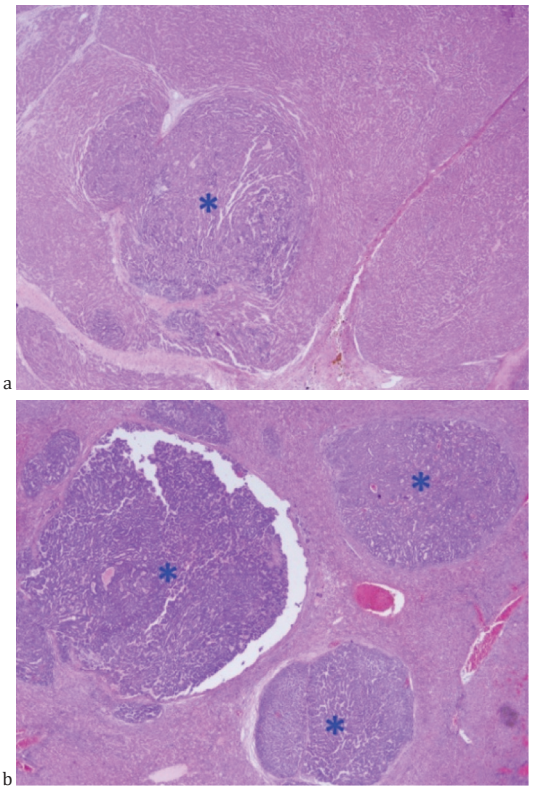

Figure 4. The main mass revealed "nodule-in-nodule" appearance (*) (a) and multiple small nodules in the remaining liver (b); (HE, 20x).

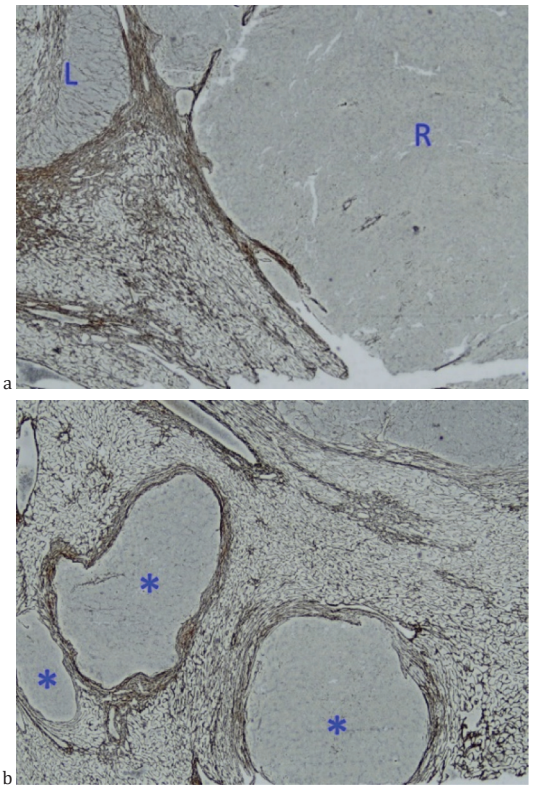

Figure 5. The reticulin framework of the nodules on the right (R) was totally lost but remained intact in nodule on the left (L) (a). Some small nodules in the remaining liver revealed total loss of reticulin framework, consistent with hepatocellular carcinoma (b); (HE, 20x).

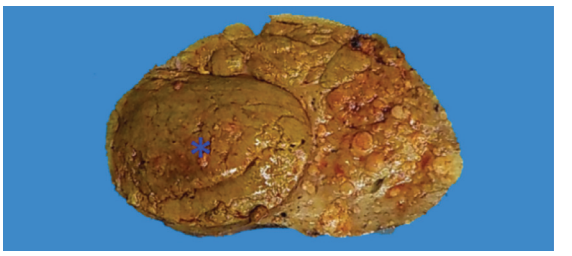

Figure 6. The macroscopic finding of the explant liver revealed a large main mass (*) with multiple small nodules in the remaining liver parenchyma.

Discussion

Hepatic adenomatosis consists of 10 or more hepatic adenomas in a normal liver in the absence of glycogen storage disease or vascular disease. Hepatic adenomas are more common in females than males and are associated with oral contraceptive pill or steroid use[1]. On the contrary, hepatic adenomatosis seems to equally affect males and females[1]. The two major complications of hepatic adenomatosis are symptomatic hemorrhage and malignant transformation. Lesions greater than 5 cm., male gender, and β-catenin subtype are the major risk factors for malignant transformation[3]. The incidence of malignant transformation of hepatic adenomas is uncommon and estimated between 2.5% to 10% in the high-risk group[4-6]. A rising AFP is often not helpful for detecting malignant transformation since the AFP level is usually within normal range[7]. The treatments for malignant transformation of hepatic adenoma include surgical resection, transarterial embolization (TAE), radiofrequency ablation (RFA), and liver transplantation in selected situations. TAE is considered to be the first line for achieving hemostasis in the actively bleeding patient[8]. RFA can be used in the small adenoma where resection is indicated but not applicable due to the location or patient's characteristic.

The present patient had liver nodule biopsies done on two separated occasions and the biopsies did not show any malignant transformation. Her AFP was elevated, and immunohistochemistry of her liver nodule biopsy showed β-catenin subtype,

which significantly increased risk of malignant transformation. The extent of her tumor precluded her from surgical resection. Liver transplantation was the only option for treatment of her hepatic adenomatosis.

Liver transplantation is usually reserved for decompensated liver disease or HCC. The first patient that underwent liver transplantation in Thailand was in 1990. However, there are not many patients without portal hypertension or cirrhosis who have had liver transplantation in Thailand. Treatment of hepatic adenoma is mostly with surgical resection. Liver transplantation is preserved only for hepatic adenoma unsuitable for resection. Most of the data collection from this group of patients are retrospective case review. Out of 17 cases of liver transplantation for hepatic adenomatosis reviewed in 2005, outcome and survival were known in 10 patients[7]. There were three patients who had HCC and adenomatosis. Two out of three died from HCC 12 years after liver transplantation and one was alive with HCC after transplantation for 27 months. In a more recent retrospective data review from European Liver Transplant Registry (ELTR) from 1986 to 2013, 64 patients had liver transplantation for hepatic adenomatosis. There was no patient lost to follow-up in the present study. The median duration of survival was 108 months (24 to 168 months) with a range of 0 to 316 months. Three patients died within 90 days from operative related complications. Indications for liver transplantation were suspicion for malignant transformation in 15 (31%) patients, HCC with histology proven in 16 (33%), disease progression in eight (16%) patients, and hemorrhagic manifestation in five (10%). Seventeen patients had confirmed HCC in their explanted livers[9]. Eight patients out of 17 had multifocal HCC. Three out of 17 patients had HCC recurrence and died of the disease.

Lynch syndrome is the autosomal dominant disease caused by heterozygous germline mismatch repair gene mutation and biallelic germline mismatch repair gene mutation. Lynch syndrome is caused by a large number of heterozygous germline mutation in MLH1, MSH2, MSH6, PMS2, and EPCAM, and is the most common cause of inherited colorectal cancer[10]. There are reports of hepatic adenoma in three unrelated patients with biallelic mismatch repair deficiency (BMMRD)[11]. The present patient had genetic consultation as a part of her transplantation work up. Her genetic testing revealed heterozygous PMS2 mutation, c.2380C>T. Her colonoscopy after transplantation was normal and did not reveal any polyp. The three patients from the previous report were homozygous PMS2 mutations[11].

Conclusion

Physicians should consider liver transplantation as the option for treatment for the patient with large multiple unresectable hepatic adenomas who is a good candidate for liver transplantation.

What is already known on this topic?

Hepatic adenomatosis is defined as 10 or more hepatic adenoma in a normal liver. Most are asymptomatic. The complications of spontaneous bleeding or malignant transformation are common in hepatic adenomatosis.

What this study adds?

Liver transplantation could be offered as the rescue therapy for hepatic adenomatosis in patients who are not a candidate for surgery or have failed embolization.

Conflicts of interest

The authors declare no conflict of interest.

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