Two cases of hepatocellular adenomatosis treated with transcatheter arterial embolization

Sawako Kobayashi · Hiroki Sakaguchi · Masaki Takatsuka ·
Takehisa Suekane · Shuji Iwai · Hiroyasu Morikawa ·
Masaru Enomoto · Akihiro Tamori · Norifumi Kawada

Received: 17 August 2008 / Accepted: 11 February 2009 / Published online: 5 March 2009
© Asian Pacific Association for the Study of the Liver 2009

Abstract Hepatocellular adenoma is a rare benign tumor of the liver. However, some complications, such as hemorrhage, rupture, and malignant transformation, have been reported previously. Surgical resection is considered to be the best choice of treatment, when adenomas are increasing in size, while resection is difficult to perform when multiple adenomas develop throughout the liver. Here, we report two cases of multiple hepatocellular adenomatosis. One patient had a history of aplastic anemia and the other had glycogen storage disease. We treated them with transcatheter arterial embolization (TAE) to prevent hemorrhage and rupture. After TAE, most parts of the adenomas showed necrotic change. These cases suggest that TAE is an effective treatment of hepatocellular adenomatosis.

Keywords Liver · Benign tumor · Rupture · Resection · Aplastic anemia · Glycogen storage disease

Introduction

Hepatocellular adenoma (HCA) is a rare benign neoplasm that is usually found in young women who are taking oral contraceptives [1–3]. It also occurs in association with the use of anabolic androgenic steroids and with type I

glycogen storage disease [4–7], while the mechanism of its tumorigenicity is unknown.

Although HCA is usually solitary, multiple adenomas have been described ranging from two nodules to multiple or disseminated lesions of various sizes. The latter is termed hepatic adenomatosis [5, 8, 9]. Although most cases of adenomas are asymptomatic and detected incidentally, HCA may undergo rupture and lead to life-threatening hemorrhage [10, 11]. Malignant transformation of HCA has also been reported [11–13]. Furthermore, HCA is difficult to distinguish clinically from a well-differentiated hepatocellular carcinoma (HCC) [5, 14]. Thus, in patients with the risk of rupture, hemorrhage, or malignant transformation, HCA must be diagnosed and treated as early as possible.

Here we report two cases in which hepatocellular adenomatosis was treated with transcatheter arterial embolization (TAE).

Case reports

Case 1

A 44-year-old woman who had been undergoing treatment of aplastic anemia with steroid and repeated blood transfusions, presented with upper abdominal pain. After clinical screening at another hospital, she was referred to our university hospital for the evaluation of multiple liver masses.

Her physical examinations were normal, except that the liver edge was palpable at 4–5 cm below the right costal margin.

A laboratory workup showed pancytopenia and elevated ferritin level (10,673.3 ng/ml). Tumor markers, such as

S. Kobayashi · H. Sakaguchi · M. Takatsuka · T. Suekane ·
S. Iwai · H. Morikawa · M. Enomoto · A. Tamori ·
N. Kawada (✉)
Department of Hepatology, Graduate School of Medicine,
Osaka City University, 1-4-3, Asahimachi, Abeno,
Osaka 545-8585, Japan
e-mail: kawadanori@med.osaka-cu.ac.jp

α -fetoprotein (AFP), protein-induced vitamin K absence or antagonist-II (PIVKA-II), and carcinoembryonic antigen (CEA), were within normal limits. Assays for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis C antibody were negative.

Computed tomography (CT) of the abdomen showed multiple space-occupying lesions throughout the liver. The masses varied in size, and the largest was $6.4 \times 4.0 \text{ cm}^2$ in diameter (Fig. 1a). Dynamic CT revealed enhancement of the masses during the arterial phase (Fig. 1b), which showed low density during the late phase (Fig. 1c). A subcapsular intrahepatic hematoma was also identified (Figs. 1a–c). The tumors were high intensity on T1 and were isointensity on T2-weighted magnetic resonance imaging (MRI). Ultrasonography showed multiple hyper-echoic and hypoechoic lesions in the liver. Abdominal angiography showed multiple hypervascular tumors in the

liver. CT during hepatic arteriography (CTA) showed these lesions with increased arterial supply (Fig. 2a), which reduced portal supply on CT during arterial portography (CTAP) (Fig. 2b). The largest tumor in the right lobe had feeding arteries running from the surrounding to the center of the tumor (Fig. 2c), compatible with a diagnosis of hepatocellular adenomatosis. Because of the risk of rupture and hemorrhage, the patient was treated with TAE with gelatin sponge alone for the largest tumor in the right lobe (Fig. 2d). A dynamic CT 7 days after TAE showed necrotic change and no early enhancement in the tumor (Fig. 3). After TAE, a tissue specimen of the tumor that was not treated with TAE obtained by fine-needle biopsy was studied microscopically. The tumor cells were mostly normal in size. Their nuclei were round and regular in size and their cytoplasm was eosinophilic. The tumor cells showed psuedo-glandular structure and no portal triads

Fig. 1 CT scan of the abdomen showing multiple space-occupying lesions in the liver (a). The masses were enhanced during arterial phase (b) and became low density during late phase (c). A subcapsular intrahepatic hematoma is seen on the surface of the right lobe (arrows)

Fig. 2 Abdominal angiography shows multiple hypervascular tumors in the liver. CT scan during hepatic arteriography shows that these mass lesions have increased arterial supply (a) and reduced portal supply on CT during arterial portography (b). The large tumor in the right lobe has feeding arteries running from the surrounding to the center of the tumor (arrowhead) (c). After TAE of the feeding artery, no tumor stain (arrowhead) is seen (d)

Fig. 3 Early-phase dynamic CT obtained after treatment shows that the tumor is not enhanced, indicating complete necrosis of the lesion

were observed in the tumor. The nontumor part of the liver showed marked hepatocellular and reticuloendothelial hemosiderosis (Fig. 4). The pathological diagnosis was hepatocellular adenomatosis in secondary hemosiderosis of the liver due to repeated blood transfusions. About 2 years after TAE, she died of heart failure, without showing the increase in the size or the rupture and hemorrhage of the masses.

Case 2

An 18-year-old man with a history of glycogen storage disease-Ia was referred to our university hospital for the evaluation of multiple liver masses. These liver masses

Fig. 4 H&E-stained section of the tumor obtained by fine-needle biopsy. The tumor cells mostly are normal in size. Their nuclei are round and regular in size and their cytoplasm is eosinophilic. The tumor cells show a pseudo-glandular structure and no portal triads are observed in the tumor. The pathological diagnosis is hepatocellular adenomatosis in the liver. Magnification: $\times 100$

were seen initially when he was 16 years old. A tissue specimen of the tumor obtained laparoscopically did not show malignant cells at that time. At the age of 18, MRI showed an increase in the size of the masses, one of which in segment 6 grew out of the liver. Therefore, the patient was admitted for further examination.

Results of his physical examination were normal, except that the liver edge was palpable below the right costal margin.

A laboratory workup showed mild anemia, mild abnormality of liver function, and hyperlipidemia. Serum AFP, PIVKA-II, and CEA were within normal limits. Assays for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis C antibody were negative.

A CT scan of the abdomen showed multiple enhancing hypervascular lesions throughout the liver. The largest in segment 4 was 5 cm in the longest diameter. Some were mildly enhanced at the late phase of dynamic study and had capsules. A tumor in segment 6 was 4 cm in diameter and grew out of the liver (Fig. 5a–c). The tumors were high intensity on T1- and T2-weighted MRI. Abdominal angiography showed multiple hypervascular tumors in the liver. These mass lesions had increased arterial supply on CTA (Fig. 6a) and reduced portal supply on CTAP (Fig. 6b). Feeding arteries of the tumor in segment 6 ran into the center after running around the tumor (Fig. 6c). On the basis of these findings, the tumors were diagnosed as hepatocellular adenomatosis. Because of the risk of rupture and hemorrhage, the patient was treated with TAE with gelatin sponge and lipiodol for the tumor in segment 6 that grew out of the liver. A dynamic CT 10 days after TAE showed lipiodol deposition and no early enhancement in the tumor (Fig. 7). We followed up him for about 1 year after TAE. The masses showed neither increase in the size nor the rupture and hemorrhage of the masses.

Discussion

Hepatocellular adenoma is a rare benign disease and occurs in association with steroid use, type I glycogen storage disease, and hemochromatosis. It shows a slow progression but sometimes causes rupture, hemorrhage, and malignant transformation [1–13]. Moreover, differential diagnosis of HCA from focal nodular hyperplasia and well-differentiated HCC is sometimes difficult [5–14]. Therefore, hepatectomy is performed in patients in which HCA increases in size [11, 15, 16]. Liver transplantation is also considered as a therapy for HCA [16]. However, because it is difficult or impossible to perform hepatectomy or liver transplantation in some cases, for instance, cases of multiple HCAs in the liver, an alternative treatment of this disease is necessary.

Fig. 5 CT scan of the abdomen showing a tumor in segment 6 of the liver (a). The tumor is enhanced during the arterial phase (b) and becomes low density during the late phase (c)

Fig. 6 CTA showing the mass lesion with increased arterial supply (a), which reduces the portal supply on CTAP (b). Feeding arteries of a tumor in segment 6 run into the center after running around the tumor (arrowhead) (c)

Hepatocellular adenomas have a wide spectrum of angiographic appearances. Tumors may indicate either hypovascularity or hypervascularity. However, hypervascular HCA has hepatic arterial branches entering from the periphery. A previous report showed that TAE could be used in patients with HCA to both facilitate surgical resection and avoid hemorrhage [17]. In fact, ruptured HCAs were treated by TAE before surgery in some cases. However, there are no reports of HCA treated with TAE except for cases that had been diagnosed as HCC before surgery [18].

To the best of our knowledge, this report is the first on the use of TAE in patients with hepatocellular

adenomatosis, diagnosed precisely before treatment. Case 1 was reported for a patient who showed multiple adenomatosis with a history of aplastic anemia, and case 2 was reported for a patient who showed multiple adenomatosis with a history of glycogen storage disease-Ia. In case 2, histology of the tumors was not available, but we diagnosed the tumors as hepatocellular adenomatosis on the basis of his clinical course and the angiography image that showed feeding artery ran into the center after running around the tumor. It was considered difficult to perform hepatectomy for these patients with multiple HCAs. As most parts of the tumors showed necrotic change after TAE, TAE is considered to be an effective therapy for

Fig. 7 Early-phase dynamic CT obtained after treatment shows lipiodol deposit and no early enhancement in the tumor. It shows necrotic change in the tumor after TAE

hepatocellular adenomatosis at least with respect to short-time efficacy as shown here. Studies to establish the long-time efficacy of TAE against HCA and adenomatosis remain as a future work.

Because the method of TAE for HCA had not been established when we treated these two patients with TAE, we chose TAE with gelatin sponge alone for case 1 and TAE with gelatin sponge and lipiodol for case 2. However, we now think that the use of lipiodol is not necessary because chemotherapeutic agents are not used for HCA. In addition, in these 2 cases, we selected segmental TAE targeted for large tumors to avoid a risk of rupture and achieved successful treatment without any complications. Since efficacy and safety of TAE against HCA via total hepatic artery have remained to be established and it is considered that repeated TAE may cause arterial damage, we propose that TAE for HCA should be limitedly considered for large tumors having a risk of rupture.

In conclusion, we showed two patients in whom hepatocellular adenomatosis was treated with TAE. This report suggests that TAE is effective for hypervascular hepatocellular adenomatosis to prevent rupture and hemorrhage when it is difficult to perform hepatectomy.

References

1. Rooks JB, Ory HW, Ishak KG, Strauss LT, Greenspan JR, Hill AP, et al. Epidemiology of the hepatocellular adenoma: the role of oral contraceptive use. *JAMA* 1979;242:644–648
2. Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PFII. Hepatic adenoma and focal nodular hyperplasia:

- clinical, pathologic and radiologic features. *Gastroenterology* 1983;84:994–1002
3. Bühler H, Pirovino M, Akobiantz A, Altorfer J, Weitzel M, Maranta E, et al. Regression of liver cell adenoma. A follow-up study of three consecutive patients after discontinuation of oral contraceptive use. *Gastroenterology* 1982;82:775–782
4. Brophy CM, Bock JF, West AB, McKhann CF. Liver cell adenoma: diagnosis and treatment of a rare hepatic neoplastic process. *Am J Gastroenterol* 1989;84:429–432
5. Wanless IR. Benign liver tumors. *Clin Liver Dis* 2002;6:513–526
6. Mergo PJ, Ros PR. Benign lesions of the liver. *Radiol Clin North Am* 1998;36:319–331
7. Volmar KE, Burchette JL, Creager AJ. Hepatic adenomatosis in glycogen storage disease type Ia: report of a case with unusual histology. *Arch Pathol Lab Med* 2003;127:e402–e405
8. Flejou JF, Barge J, Menu Y, Degott C, Bismuth H, Potet F, et al. Liver adenomatosis. An entity distinct from liver adenoma? *Gastroenterology* 1985;89:1132–1138
9. Chiche L, Dao T, Salamé E, Galais MP, Bouvard N, Schmutz G, et al. Liver adenomatosis: reappraisal, diagnosis, and surgical management: eight new cases and review of the literature. *Ann Surg* 2000;231:74–81
10. Fulcher AS, Sterling RK. Hepatic neoplasms: computed tomography and magnetic resonance features. *J Clin Gastroenterol* 2002;34:463–471
11. Ribeiro A, Burgart LJ, Nagorney DM, Gores GJ. Management of liver adenomatosis: results with a conservative surgical approach. *Liver Transpl Surg* 1998;4:388–398
12. Talente GM, Coleman RA, Alter C, Baker L, Brown BI, Cannon RA, et al. Glycogen storage disease in adults. *Ann Intern Med* 1994;120:218–226
13. Grazioli L, Federle MP, Ichikawa T, Balzano E, Nalesnik M, Madariaga J. Liver adenomatosis: clinical, histopathologic, and imaging findings in 15 patients. *Radiology* 2000;216:395–402
14. Kebapci M, Kaya T, Aslan O, Bor O, Entok E. Hepatic adenomatosis: gadolinium-enhanced dynamic MR findings. *Abdom Imaging* 2001;26:264–268
15. Ault GT, Wren SM, Ralls PW, Reynolds TB, Stain SC. Selective management of hepatic adenomas. *Am Surg* 1996;62:825–829
16. Leese T, Farges O, Bismuth H. Liver cell adenomas. A 12-year surgical experience from a specialist hepato-biliary unit. *Ann Surg* 1988;208:558–564
17. Luigi G, Federle MP, Brancatelli G, Ichikawa T, Olivetti L, Blachar A. Hepatic adenomas: imaging and pathologic findings. *RadioGraphics* 2001;21:877–892
18. Hsu CY, Chu CH, Lin SC, Yang FS, Yang TL, Chang KM. Concomitant hepatocellular adenoma and adenomatous hyperplasia in a patient without cirrhosis. *World J Gastroenterol* 2003;9:627–630