Spontaneous regression of tumors is an extremely rare event in hepatocellular carcinoma (HCC) with only a few reports available. With the accumulation of clinical information and tumor immunogenetics, several mechanisms for the cystic changes of HCC have been suggested, including arterial thrombosis, inflammation, and rapid tumor growth. This paper reports an uncommon case of partial regression of HCC, which was initially misdiagnosed as a mucinous cystic neoplasm of the liver due to the unusual radiologic findings. A 78-year-old female with the hepatitis B virus and liver cirrhosis presented with an approximately 5 cm-sized cystic mass of the liver. From the radiologic evidence of a papillary-like projection from the cyst wall toward the inner side, the initial impression was a mucinous cystic neoplasm of the liver. The patient underwent a surgical resection and finally, cystic degeneration of HCC, in which approximately 80% necrosis was noted. This case suggests that if a cystic neoplasm of liver appears in a patient with a high risk of HCC on a hepatobiliary imaging study, it is prudent to consider the cystic degeneration of HCC in a differential diagnosis. (Korean J Gastroenterol 2019;73: 303-307)

Key Words: Liver neoplasms; Magnetic resonance imaging; Diagnostic errors

INTRODUCTION

Despite the burgeoning development of imaging technology, it is still difficult to differentiate between malignant and benign mass-like cystic hepatic lesions of chronic liver disease, such as liver cirrhosis. In general, distinctive and unique imaging findings of each disease have helped physicians make a correct diagnosis. On the other hand, these distinctive imaging features occasionally lead to an incorrect diagnosis. This paper describes a rare case of cystic degeneration of hepatocellular carcinoma (HCC) that was initially diagnosed as a mucinous cystic neoplasm of the liver based on the imaging study findings.

CASE REPORT

A 78-year-old woman with a history of chronic hepatitis B visited a local hospital in January 2017 for a regular liver check-up. The CT scan revealed a single cystic mass at liver segment 5/8. Two weeks later, she visited the outpatient department for a further evaluation. She looked well and only reported continuous fatigue in daily life. A phys-
Fig. 1. Computed tomography scan shows ill-defined, 4×5 cm sized cystic mass located in segment V/VIII with peripheral enhancement in the arterial phase, panel (A) and venous phase, panel (B).

Ultrasonography provided further information on the lesion: a coarse liver surface and diminished volume, indicating liver cirrhosis. The cystic mass showed hypovascularity using the Doppler method. The internal echogenicity was more heterogeneous than the CT finding.

MRI revealed a cystic mass with heterogeneous signal intensity on the T1-weighted images and T2-weighted images, but high signal portions of the heterogeneous pattern were strengthened on the T2-weighted image. A dynamic MRI scan showed an enhanced mural nodule on the edge of the cyst in the arterial phase that faded in the following venous phase. In the two-minute delayed phase, enhanced papillary-shaped projections from the cystic wall emerged. Interestingly, this enhanced papillary pattern became clearer in the five-minute delayed phase. The papillary projections faded in the hepatobiliary phase. On a diffusion-weighted image, most portions inside the cyst revealed decreasing signal intensity because the B value increased from low to high. On the other hand, a few spot-like lesions changed from a low signal to a high signal as the B value increased (Fig. 2). Overall, considering the enhanced mural nodule, papillary projections, and heterogeneous internal component, a tentative diagnosis of mucinous cystic neoplasm of the liver was first made. Because the enhancing mural nodule showed an early enhancing-early fading pattern like the typical enhancement pattern of HCC, an atypical form of HCC could not be excluded completely. A surgical resection was decided to confirm the diagnosis and determine a treatment plan.

In February 2017, partial resection of segment 5/8 of the liver was conducted. A gross examination revealed the excised liver tissue to be a relatively pale, brownish necrotic mass measuring 4.7×4.3 cm in cross-section with yellowish nodular lesions and cirrhotic changes along the peripheral portion. Focally cystic areas containing serous fluid or hemorrhagic necrotic debris were observed. The surgical margin was not...
Fig. 2. Dynamic magnetic resonance imaging shows; pre-enhancement phase (A), arterial phase (B), portal phase (C), papillary-shaped projection from cyst wall toward the inner side at two-minute delay phase (D).

Fig. 3. Remnant hepatocellular carcinoma cell surrounding broad necrosis (A, H&E, ×40), pleomorphic and undifferentiated malignant cell (B, H&E, ×200).
involved grossly. Microscopically, 80% of the mass was necrotized, and viable tumor tissue along the peripheral portion indicated an Edmondson grade III, trabecular or solid type HCC (Fig. 3). Microvessel invasion was noted, but no fatty changes within the tumor tissue were observed. The papillary-shaped projection was a fibrous capsule facing the inner side of the cyst. Cirrhotic changes were also found outside the mass. Five days postoperatively, bile duct leakage via the drainage tube was noted. Subsequently, the patient underwent an insertion of an endoscopic nasobiliary tube to treat this complication. After the procedure, no other complications occurred. She was discharged in good condition.

DISCUSSION

Cystic degeneration is one of the rare manifestations of HCC. Numerous mechanisms for cystic changes of HCC have been suggested, including arterial thrombosis, inflammation, rapid tumor growth, and androgen therapy, but the precise mechanism has not been elucidated. Some authors hypothesized immune-related mechanisms, in which interleukin-18 induces the release of interferon-γ from T lymphocytes and natural killer cells, resulting in cell-mediated tumor necrosis. Pathological evidence of the inflammatory response to tumor necrosis accompanied by the rapid infiltration of leukocytes or massive lymphoid infiltration have been reported. Given the tumor size and absence of any lymphocyte infiltration in this patient, the mechanism was speculated to be local ischemia due to rapid tumor growth or that a disruption of the feeding artery resulted in intratumoral bleeding and hemorrhagic necrosis. Unfortunately, the disruption of the feeding artery could not be confirmed by angiography.

Spontaneous regression of HCC has been reported intermittently since the 1950s. Cystic changes before a complete or partial regression do not always occur. Therefore, liquefactive necrosis is not necessary for regression. In that case, another cell death mechanism, such as apoptosis or autophagy, might be the main mechanism of regression, even though most hepatic cancer cells are resistant to tumor necrosis factor-related and apoptosis-inducing ligand-induced apoptosis. Moreover, it is unknown if partial regression must progress to complete regression. In this regard, further study is needed to determine if the cystic changes in HCC are related to a string of processes toward complete spontaneous regression. Recently, increasing understanding of tumor immunogenicity shows a promising result of novel classes of immune-targeted therapies. Therefore, it is important to unify the concepts of the mechanism of HCC regression at this juncture.

HCC in patients with chronic liver disease is confidently diagnosed without a histology confirmation because of the characteristic vascular patterns on CT and MRI owing to the recent advances in imaging technology and increasing interpretation of the surveillance of high-risk populations. On the other hand, atypical radiology findings of HCC are difficult to diagnose solely by imaging. Accordingly, radiological differentiation is very important when physicians encounter cystic neoplastic lesions with chronic liver disease, such as liver cirrhosis, on an imaging study. Similar to the present case, it might be difficult to distinguish between mucinous cystic neoplasms of the liver and cystic degeneration of HCC, unless it exhibits its own key radiologic features. Although cystic degeneration of HCC is rare, its distinctive radiologic pattern has been reported: an irregular, multilocular, hypoattenuating lesion with peripheral ring enhancement. The pattern of images is believed to be a linkage to the pathologic features of central necrosis and remnant surrounding malignant cells. Moreover, the image findings of mucinous cystic neoplasm of the liver are similar to cystic HCC in the view of multiloculation and peripheral enhancement. Fine septation and variable calcification strongly suggest a mucinous cystic neoplasm of the liver rather than cystic HCC. In the present case, as peripheral enhancement was observed, not multiloculation or calcification, the authors’ focused on the papillary-shaped projection from the cyst wall. The papillary-shaped projection showed maximum intensity in the delayed phase. Based the papillary-shaped projection and heterogeneous pattern, the patient was diagnosed initially with mucinous cystic neoplasm of the liver with internal hemorrhage rather than atypical vascularized cystic HCC. On the other hand, the histological examination indicated that the papillary-shaped projection was a fibrous capsule facing the inner side of the cyst that received portal venous blood. The heterogeneity turned out to be hemorrhage, fibrosis, and necrotic debris on a gross examination. A mosaic or heterogeneous pattern was noted when the cyst contained fibrosis, hemorrhage, arteriovenous shunting, and intramural necrosis.

To the best of the authors’ knowledge, this patient had rare cystic HCC; only a few similar cases have been described.
As in this case, cystic degeneration of HCC can be misdiagnosed radiologically as mucinous cystic neoplasm of the liver. Regarding the cystic degeneration of HCC, although theories of immune activation, androgen effects, apoptosis, inflammation, and other factors have been proposed, no definitive explanation of its mechanism has been established. In a pathological perspective, it is worth delving deeper into the mechanism of cystic HCC to switch to molecular-targeted therapeutic strategy in the future.

REFERENCES

1. Gonwa ME, Casillas J, Livingstone AS, Robinson PG. Cystic hepatocellular carcinoma: CT findings. J Comput Assist Tomogr 1991;15:1045-1047.
2. Yoo YJ, Kim JH. Spontaneous complete remission of hepatocellular carcinoma. Korean J Gastroenterol 2015;66:359-362.
3. Abiru S, Kato Y, Hamasaki K, Nakao K, Nakata K, Eguchi K. Spontaneous regression of hepatocellular carcinoma associated with elevated levels of interleukin 18. Am J Gastroenterol 2002;97:774-775.
4. Park HS, Jang KY, Kim YK, Cho BH, Moon WS. Hepatocellular carcinoma with massive lymphoid infiltration: a regressing phenomenon? Pathol Res Pract 2009;205:648-652.
5. Gottfried EB, Steller R, Paronetto F, Lieber CS. Spontaneous regression of hepatocellular carcinoma. Gastroenterology 1982;82:770-774.
6. Sun J, Yu X, Wang C, et al. RIP-1/c-FLIPL induce hepatic cancer cell apoptosis through regulating tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Med Sci Monit 2017;23:1190-1199.
7. Parks AL, McWhirter RM, Evason K, Kelley RK. Cases of spontaneous tumor regression in hepatobiliary cancers: implications for immunotherapy? J Gastrointest Cancer 2015;46:161-165.
8. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.
9. Falidas E, Pazidis A, Anyfantakis G, Vlachos K, Goudeli C, Villias C. Multicystic hepatocarcinoma mimicking liver abscess. Case Rep Surg 2013;2013:374905.
10. Hagiwara S, Ogino T, Takahashi Y, et al. Hepatocellular carcinoma mimicking liver abscesses in a cirrhotic patient with severe septic shock as a result of salmonella O9 HG infection. Case Rep Gastroenterol 2009;3:56-60.
11. Choi BI, Lim JH, Han MC, et al. Biliary cystadenoma and cystadenocarcinoma: CT and sonographic findings. Radiology 1989;171:57-61.
12. Kim SH, Jeong WK, Kim Y, et al. Hepatocellular carcinoma composed of two different histologic types: imaging features on gadobetic acid-enhanced liver MRI. Clin Mol Hepatol 2013;19:92-96.