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Mucinous Cystic Adenoma of the Liver: A Thought-Provoking Case of an Uncommon Hepatic Neoplasm

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 70-year-old
Final Diagnosis: Liver disease
Symptoms: Asymptomatic
Medication: —
Clinical Procedure: Hepatectomy
Specialty: Gastroenterology and Hepatology

Objective: Rare disease
Background: Mucinous cystic neoplasm (MCN) of the liver is a rare hepatic neoplasm: a cystic, mucus-producing tumor. Histopathologic examination reveals ovarian-like stroma. The origin of MCN of the liver is still unknown, although ectopic ovarian-like stroma in the liver has been suggested as a possibility. We document a thought-provoking case of MCN of the liver, and intratumoral fatty tissue may support the opinion that ectopic ovarian-like stroma in the liver is a possible origin for both MCN and ovarian teratoma.

Case Report: An expansive 10.5-cm cystic tumor was incidentally detected in a 71-year-old woman. Imaging studies revealed that the tumor was multiloculated, with cyst contents comprising mucus, muddy-looking fluid (inspissated bile), and hematoma. Imaging studies revealed fatty tissue and calcifications in the cyst walls. The diagnosis of MCN of the liver was made, although MCNs have never been reported to include fatty tissue. Extended left lobectomy was performed, and the tumor was curatively removed without any rupture. A multilocular cyst, mucus, calcifications, and fatty tissue were clearly observed on gross inspection. Histopathological examination revealed ovarian-like stroma. Evidence of malignancy was not detected. Her postoperative course was uneventful. To the best of our knowledge, our patient is the first case of MCN of the liver with intratumoral fatty tissue. This case may support the hypothesis that MCN originates from ectopic ovarian-like stroma in the liver.

Conclusions: We documented a thought-provoking case of MCN of the liver in detail, and this MCN accompanied with fatty tissue might originate from ectopic ovarian-like stroma.

Keywords: Adenoma • Cysts • Liver • Liver Neoplasms • Mucus • Ovary

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Background

Mucinous cystic neoplasm (MCN) of the liver is a rare hepatic neoplasm, and this cystic, mucus-producing tumor is histopathologically associated with ovarian-like stroma [1-3]. Radical resection is curative treatment [4-7], and the postoperative prognosis is acceptable [2,3,7,8]. The origin of MCN of the liver is still unknown, although ectopic ovarian-like stroma in the liver has been suggested [8-10].

We report a thought-provoking case of MCN of the liver in detail. In general, MCN of the liver does not involve fatty tissue [3,11,12]. In particular, to the best of our knowledge, our patient is the first case of MCN of the liver having fatty tissue inside the tumor. This case may support the hypothesis

that ectopic ovarian-like stroma in the liver is the origin of MCN [8-10]. Moreover, we discuss a possible origin of an extremely rare MCN in the liver accompanied with fatty tissue, with a literature review.

Case Report

A 71-year-old woman with diabetes and deep venous thrombosis was referred to our hospital for treatment of meningitis. She had no history of smoking or excessive alcohol consumption. Treatment for meningitis resulted in drug-induced liver damage, and the liver was checked by ultrasound as part of our routine protocol in such cases. An expansive 10.5-cm cystic tumor was incidentally detected in the medial lobe of the

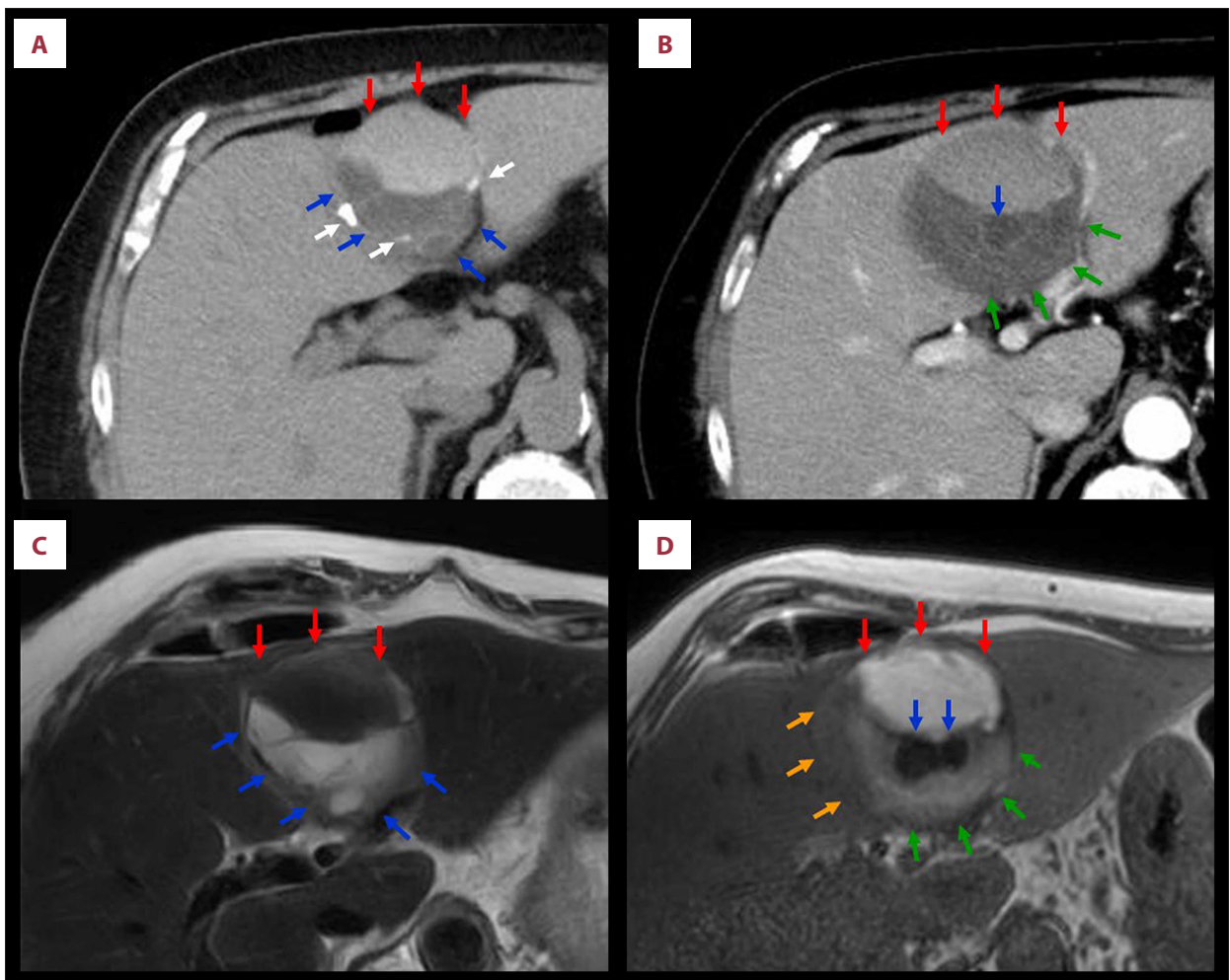


Figure 1. Hepatic CT and MRI findings. (A, B) Imaging findings of plain CT (A) and T2-weighted MRI (B). Calcifications were clearly detected on plain CT (white arrows). The multilocular cyst (ie, cyst-in-cyst) contained mucus (blue arrows). A hematoma was observed inside (red arrows). (C, D) Imaging findings of dynamic CT (C) and T1-weighted MRI (D). The cystic, mucus-producing tumor contained not only mucus (blue arrows), but also muddy-looking fluid (ie, inspissated bile) (green arrows) and hematoma (red arrows). The cyst wall did not show enhancement, and a partial solid component was observed (orange arrows). CT – computed tomography; MRI – magnetic resonance imaging.

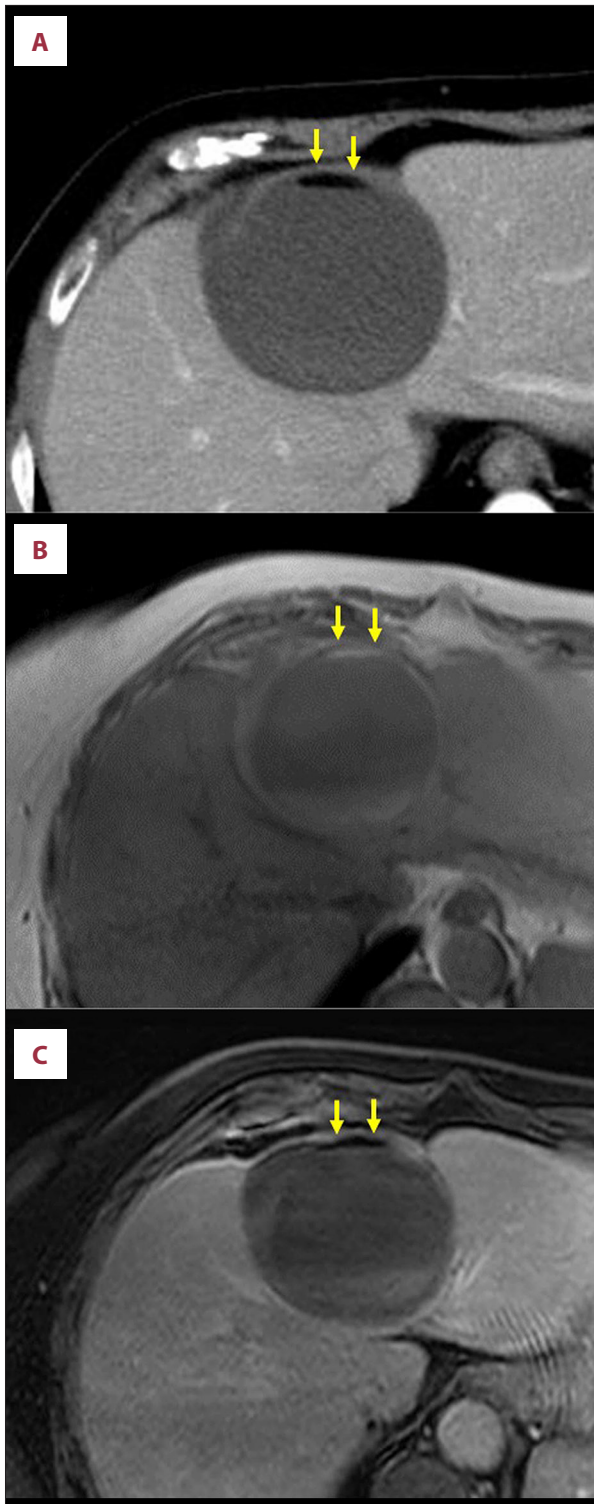


Figure 2. Fatty tissue within the cyst. Imaging findings of plain CT (A), T1-weighted MRI (B), and fat-suppressed MRI (C). The cystic, mucus-producing tumor clearly included fatty tissue (yellow arrows). CT – computed tomography; MRI – magnetic resonance imaging.

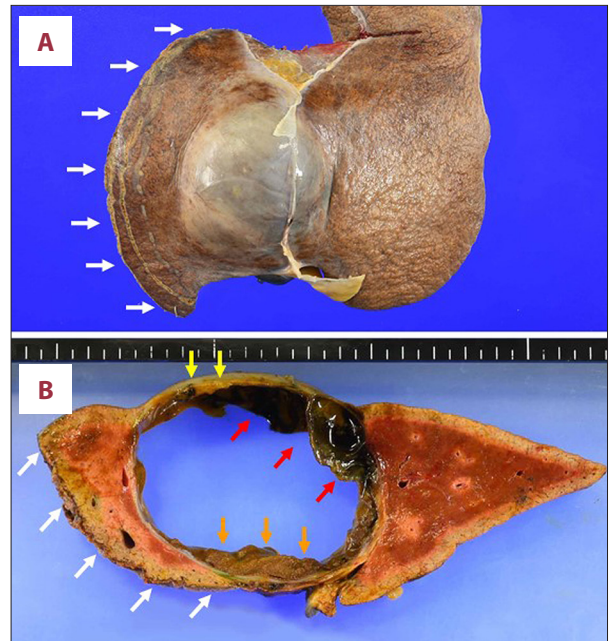


Figure 3. Gross pathological examination. Examination of the resected specimen revealed that the tumor was 10.5 cm and was curatively removed without any rupture of the cyst (overhead view, A). The cyst was multilocular, with mucus, calcifications, hematoma (red arrows), and fatty tissue (yellow arrows) observed (coronary view, B). Inspissated bile was present within the tumor. Cut surface (white arrows) is presented (A, B).

liver. Plain and dynamic computed tomography and enhanced and fat-suppressed magnetic resonance imaging revealed that this tumor was multilocular (ie, cyst-in-cyst), contained mucus, muddy-looking fluid, and hematoma (Figure 1A-1D), and was associated with fatty tissue (Figure 2) and calcifications (Figure 1A). The cyst wall did not show enhancement, but a partial solid component was observed (Figure 1D). The sharply margined cyst wall touched the middle hepatic vein. Tumor markers were all within the reference range. Splenomegaly indicated portal hypertension, although collateral development was not observed. We suggest that intratumoral bleeding, which resulted in hematoma, might secondarily cause communication with the bile duct. Hence, a diagnosis of MCN of the liver was made, although MCN has not been reported to include fatty tissue. In fact, intraductal papillary neoplasm of the bile duct (IPNB) was a differential diagnosis in our patient. Three-dimensional volumetry showed that the remnant liver volume in an extended left lobectomy was estimated to be 76.9%. The demarcation line was clearly confirmed after ligation of the left portal vein, and then, the middle and left hepatic arteries were ligated. Extended left lobectomy with resection of the middle hepatic vein and Spiegel lobe was performed, and the cystic, mucus-producing tumor was curatively removed without any rupture (Figure 3A). In order to keep a safe surgical margin

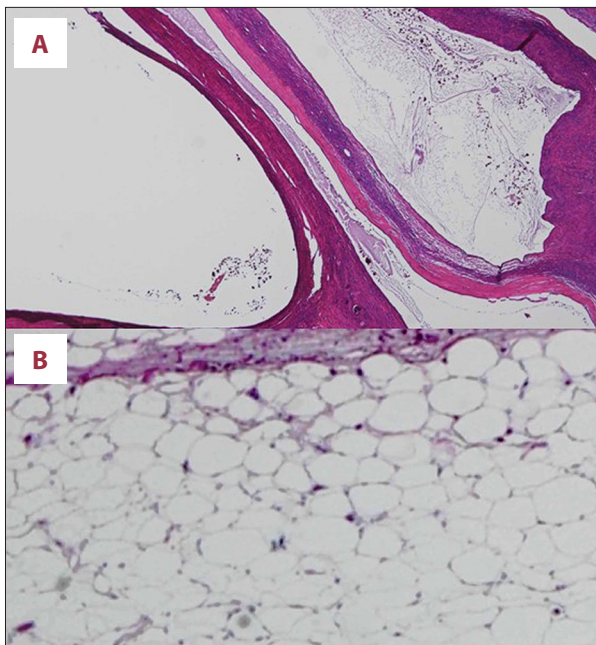


Figure 4. Histopathological examination. (A) Microscopic section of the MCN cyst wall (hematoxylin-eosin staining, ×40 magnification). Cystic wall lined by epithelial cells, and mucosal fluid was involved. (B) Fatty tissue was also observed (hematoxylin-eosin staining, ×200 magnification).

and to avoid an intraoperative rupture, we employed intraoperative ultrasound. Contrast agent (Sonazoid; GE Healthcare, Oslo, Norway) and color Doppler were also used. Hence, transection of hepatic parenchyma and the middle hepatic vein were guided in real-time during hepatectomy. The operative time was 241 minutes. Blood loss was 702 mL, and blood transfusion was not required. Gross pathologic inspection of the resected specimen revealed inspissated bile within the cystic tumor, corresponding to the muddy-looking fluid seen in pre-operative imaging studies (Figure 1C, 1D). Multiloculation, mucus, calcifications, and fatty tissue were clearly observed (Figures 3B, 4). Histopathological assessment revealed ovarian-like stroma (Figure 5), that was positive for estrogen and progesterone receptors in immunohistochemical studies (Figure 5). Evidence of malignancy was not detected. The diagnosis was MCN of the liver. Histopathologic examination of the nontumoral liver revealed cirrhosis, presumably related to metabolic disease. Her postoperative course was uneventful, and she was discharged from the hospital on postoperative day 14.

Discussion

MCN of the liver was first documented in 1958 by Edmondson [13], and its incidence is rare, at <5% of cystic diseases of the liver [7,13]. In 1985, it was reported that some

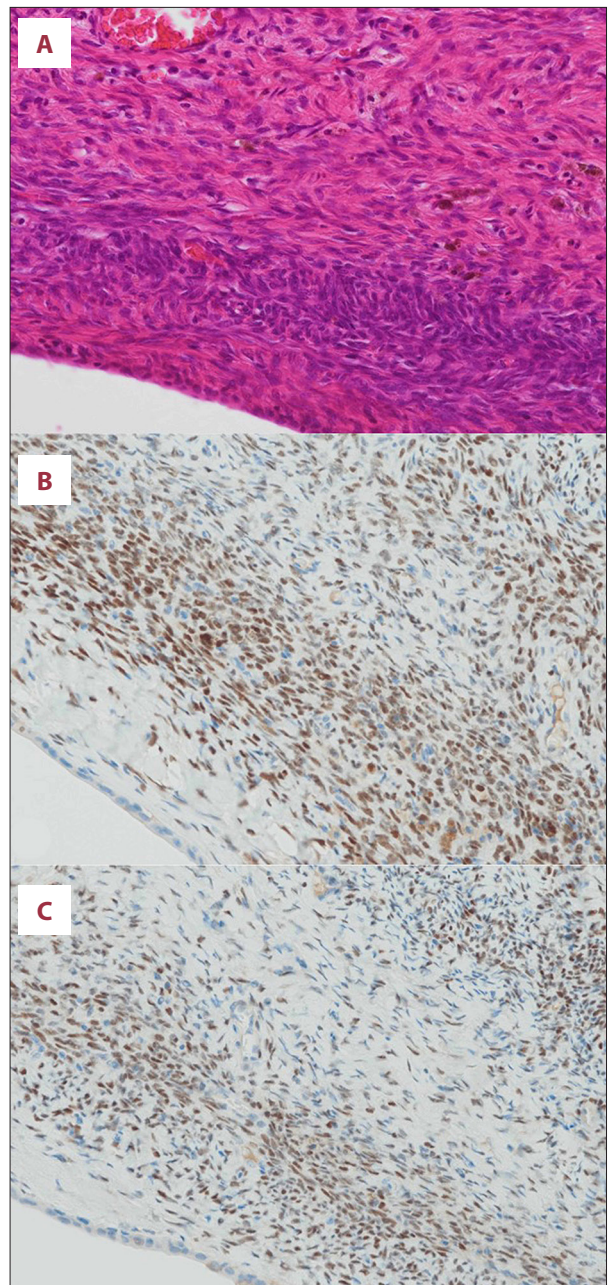


Figure 5. Ovarian-like stroma. Ovarian-like stroma was observed (hematoxylin-eosin staining, ×80 magnification) (A). Ovarian-like stroma was positive for estrogen receptor (B) and progesterone receptor (C) in immunohistochemical studies.

cystic and mucus-producing neoplasms in the liver were histopathologically associated with ovarian-like stroma [1], and thereafter, there was a period of confusion between the clinical assessment and histopathological findings. Clinical symptoms, serologic markers, and imaging modalities are unreliable for diagnosing cystic and mucus-producing neoplasms of the liver, resulting in misdiagnosis in 55-100% of these

Table 1. Diagnostic algorithm of epithelium-lined cystic lesions of the liver [2].

Cystic lesions		Ovarian-like stroma into the wall	Epithelial invasion	Pathological diagnosis
Epithelium-lined Biliary, mucinous and/or oncosystic (with or without papillary architecture)		Yes	Yes	MCN with an associated invasive carcinoma
			No	MCN
		No	Yes	Malignant IPNB Intrahepatic cholangiocarcinoma with cystic change
			No	IPNB
Ciliated	Ciliated foregut cyst		Ciliated foregut cyst	
Cuboidal and/or low columnar				Solitary bile duct cyst
				Obstructive biliary dilatation
				Others

IPNB – intraductal papillary mucinous neoplasm of the bile duct; MCN – mucinous cystic neoplasm.

patients [14,15]. Therefore, there was a great change in the disease concept and diagnostic criteria for these hepatic neoplasms. The World Health Organization (WHO) classification of digestive system tumors continually reflects important advancements in the field of clinical oncology and tumor pathology [16]. In 2010, the WHO clarified the classification of cystic and mucus-producing neoplasms in the liver and put an end to physicians' confusion and muddled pathological criteria (Table 1) [2]. Thereafter, the WHO classification is widely used for classification of epithelium-lined cystic lesions of the liver [2,3].

MCN is a cystic, mucus-producing neoplasm; it has the following clinical features and pathological characteristics: (i) significant sex-based difference in incidence (ie, occurrence mainly in women), (ii) multilocular (so-called "cyst-in-cyst") or unilocular cystic form, (iii) no communication with the bile duct, (iv) mucosal fluid, (v) wall lined by cuboidal or columnar mucus-producing epithelial cells, and (vi) histopathological confirmation of ovarian-like stroma [1-3,14,16]. In our case, inspissated bile in the MCN indicated communication with the bile duct, which we suggested might occur secondarily because of bleeding into the MCN, supported by the coexistence of hematoma. In contrast, IPNB, which is important to include in the differential diagnosis, is a biliary epithelial neoplasm that shows papillary growth on the axis of the vascular stroma into the bile duct. IPNB has the following clinical features and pathological characteristics: (i) no sex-based difference in incidence, (ii) lobulated shape, (iii) changes in the bile duct (eg, distal dilation), (iv) independent of mucus production, (v) non-invasive papillary or villous tumor, and (iv) absence of ovarian-like stroma [1-3,14,16].

Definitive diagnosis of MCN in the liver is challenging [14,15]. MCN of the liver does not involve fatty tissue [3,11,12], and generally has no communication with the bile duct. The most common differential diagnosis is IPNB [2,3,12,15]. IPNB also is accompanied by mucus production, but generally shows communication with the bile duct and/or biliary changes [1-3,14,16]. In our patient, the cystic tumor contained mucus, muddy-looking fluid (ie, bile), and hematoma. Intratumoral bleeding easily results in hematoma [17], and a bleeding episode may secondarily cause unexpected communication with the bile duct [17,18]. Even though intratumoral bleeding and biliary communication are rare in MCN, patients with MCN in the liver accompanied with intratumoral bleeding [17] and biliary communication [18] have been reported. In our patient with MCN in the liver, we considered that intratumoral bleeding might secondarily cause biliary communication. Hence, we made a preoperative diagnosis of not IPNB but MCN, although MCN in the liver never involves fatty tissue [3,11,12],

MCN of the liver has malignant potential; therefore, radical resection is the first-choice therapeutic strategy [4-7,19]. Even in cases that are malignant, MCN of the liver generally grows into its own cystic lesion [2,3]. Hence, curability can be achieved by optimal surgery even in malignant MCNs in the liver [2,3,19], and oncological and prognostic outcomes are good after radical resection [2,8,19]. Needless to say, even a subtle rupture during hepatectomy should be avoided to prevent iatrogenic dissemination, and hepatectomy procedures for surgical curability should be carefully decided on a case-by-case basis. In benign MCN, curative resection is mandatory [7,8,19] because patients with a partial remnant often have persistent symptomatic disease [2,8]. The prognosis of benign MCN after surgery

is excellent [7,8,19], and no oncological deaths have been documented. Even in malignant MCN, the 5-year survival rate after surgical resection was reported to be 68.9-100% [8,19].

MCN and IPNB are clearly classified on the basis of the presence or absence of ovarian-like stroma [1-3], and a histopathological characteristic of MCN is the presence of ovarian-like stroma in the cyst wall as aggregated spindle-shaped cells. This stroma expresses estrogen and/or progesterone receptors, although the positivity rate in immunohistochemistry is low. However, epithelial cells of the MCN produce mucus, which is the main component. From the viewpoint of immunohistochemistry of the core protein of mucin, the meaning of a specific profile of mucin expression (eg, MUC1) is controversial in MCN of the liver [20], although this expression reflects the malignant potential of cystic, mucus-producing neoplasms of the pancreas [21].

The origin of MCN of the liver is still unknown. Some hypotheses have been suggested; for example, endoblast (the source of the hepatic parenchyma and bile ducts) and ectopic ovarian-like stroma in the liver are reported to be potential sources [8-10]. MCN of the liver morphologically and embryologically recapitulates ovarian stroma [8-10]. MCN in the liver may arise from ectopic stromal cells or primitive gonadal tissue [8-10], and these may have an ability to transdifferentiate to ovarian cortical cells [8-10]. In general, teratomas arise from germ cells that originate in the mature genital glands [22,23], and extremely rare cases of teratomas at extragonadal site and/or origin have been reported [24-26]. In particular, the unique finding of fatty tissue and rare finding of calcifications in the tumor were clearly observed in our patient. To the best of our knowledge, our patient is the first case of MCN of the liver that had associated intratumoral fatty tissue (Figure 2). Calcifications were

also observed in our case. In contrast, ovarian teratomas often involve teeth, bone, skin, and hair, in addition to fatty tissue [22,23]. However, we speculate that ectopic ovarian-like stroma in the liver is a possible origin for both MCN and ovarian teratoma [8-10,22,23], and the unique finding of intratumoral fatty tissue in our case supports the possibility that ectopic ovarian-like stroma is the origin of MCN of the liver [8-10,23].

We hope that our case report will be informative for physicians, surgeons, pathologists, and radiologists in the hepatobiliary field.

Conclusions

A thought-provoking case of MCN of the liver was documented in detail. In general, MCN of the liver never involves fatty tissue, and our extremely rare case of MCN may have originated from ectopic ovarian-like stroma in the liver.

Ethics Approval

This report was approved by the Institutional Review Board of Shiga General Hospital, Moriyama, Japan.

Acknowledgment

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Conflict of Interest

None.

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