Diagnosis And Management of Intrahepatic Biliary Cystadenoma: A Single-Center Experiences And Lessons Learned

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Research Article

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Abstract

Background: Intrahepatic biliary cystadenoma (IBC) is a rare benign cystic tumor of the liver with carcinogenic potential. Due to its low incidence and lack of specific clinical symptoms and signs, IBC is easily confused with other cystic liver lesions; even today, IBC mistakenly underwent fenestration and drainage according to the hepatic cyst in adverse conditions consequences for patients.

Methods: The clinical data of six patients with pathologically defined IBC, admitted to the Department of Hepatobiliary Surgery of the Affiliated Hospital of Guangdong Medical University from January, 2011, to July, 2021 were retrospectively analyzed.

Results: Four patients (4/6) were diagnosed with IBC preoperatively, administrated the surgery, and discharged successfully. One patient underwent single-port laparoscopic fenestration and drainage of liver cyst, cyst wall biopsy, intraoperative pathology revealed IBC, then open left hemihepatectomy. Another patient underwent laparoscopic fenestration and drainage of hepatic cyst. Intraoperative pathologic diagnosis from cyst wall biopsy showed a simple hepatic cyst, but the final pathological diagnosis was IBC. The remaining liver volume was insufficient to undergo liver resection; the patient was again referred to our institution after four months with right upper quadrant pain. Computed tomography revealed extensive abdominal nodules, considered malignant transformation, and the patient died three months later.

Conclusion: Since atypical IBC is easily misdiagnosed as hepatic cysts, and we propose paying attention to cystic wall morphology and cyst fluid properties during the operation. At the same time, it is recommended that patients diagnosed with liver cysts undergo intraoperative pathological diagnosis and strengthen communication with pathologists to deepen understanding of IBC, which avoids missed diagnosis, wrong operation, or even secondary operation.

Background

Intrahepatic biliary cystadenoma (IBC) is a rare benign cystic tumor of the liver with carcinogenic potential. The tumor originates from the bile duct epithelium and is lined by mucus-secreting columnar or cuboidal epithelium. Due to its low incidence, lack of specific clinical symptoms and signs, and insufficient attention, IBC is easily confused with other cystic lesions of the liver; as such, treatment is often delayed or improper. The clinical data of six patients with pathologically confirmed IBC admitted to the Department of Hepatobiliary Surgery of the Affiliated Hospital of Guangdong Medical University between January, 2011 and July, 2021 were reviewed and reported as follows to enhance the knowledge of this disease and provide experience for clinical diagnosis and treatment.

Materials And Methods

Patients

The clinical data of six patients with pathologically confirmed IBC admitted to the Department of Hepatobiliary Surgery of the Affiliated Hospital of Guangdong Medical University between January, 2011 and July, 2021. This study was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Guangdong Medical University.

General Information Of Patients

Six patients include two males and four females; male: female incidence ratio=1:2; age range 41–67 years; median age 54.7±11.9 years. Clinical findings: One patient presented with abdominal pain (1/6), while the remaining five were found

to have cystic liver occupancy on physical examination, and further hospitalized for surgery at a later stage due to progressive enlargement of the cystic mass, with clinical discomfort (3/6). The liver and kidney functions were normal in all the patients except for one who presented with hepatitis B virus surface antigen-positivity; the other five patients were negative for hepatitis virus markers. The detecting key levels of APF and CA125 were within the normal range; CA199 was abnormal in two (2/6) cases, while the carcinoembryonic antigen (CEA) level was also abnormal in two (2/6) cases. The general information of patients is showed (Table 1).

Table 1
Clinical data of six patients with IBC

Case no.	Age /sex	Clinical findings	Tumor location	Tumor size	tumor markers		Method of diagnostic Imaging	Preoperative diagnosis
					CA199 (0-27.0U/ml)	CEA (0-5.0ng/ml)		
1	67 M	Abdominal mass (physical examination)7 days	left lateral lobe	10cm×7cm ×7.4cm	3.3	4.5	MRI	IBC
2	50M	Abdominal mass (physical examination) 3 days	right lobe	48mm×34mm ×49mm	15.0	7.3	CT/MRI/ CEUS	IBC
3	41F	Abdominal mass (physical examination) 2 years, right upper abdominal pain 1 month	right lobe	15cm×10cm ×14cm	5.8	3.6	CT	IBC
4	66 M	Right upper abdominal pain 2 months	left medial lobe and right anterior lobe	17cm× 14cm ×15cm	10.5	14.3	CT	liver cyst
5	62 M	Abdominal mass(physical examination) 7 years, right upper abdominal pain 2 months	right lobe	8.5cm×8.3cm ×7.3cm	32.3	2.5	CT/MRI/ CEUS	IBC
6	42 F	Abdominal mass(physical examination) 4 years, right upper abdominal pain 3 months	left lateral lobe	8.2cm×8.3cm ×10.3cm	33.9	1.8	CT / CEUS	liver cyst

MRI: Magnetic resonance imaging, CT: Computed Tomography, CEUS: contrast-enhanced ultrasonography, CA 19-9 : carbohydrate antigen 19-9, CEA : carcinoembryonic antigen, IBC : intrahepatic biliary cystadenoma

Preoperative Imaging Of Patients

Preoperative abdominal imaging (color Doppler ultrasound or contrast-enhanced ultrasonography) was performed in all six patients. Preoperative diagnosis of IBC was made in four (4/6) patients, while the rest were diagnosed with a liver

cyst. Magnetic resonance imaging (MRI) examination was performed in three cases (3/6), revealing IBC. Six patients underwent preoperative computed tomography (CT) examination (one case underwent plain abdominal CT scan and the remaining five underwent contrast-enhanced CT), and preoperative diagnosis of IBC was made in three (3/6). Tumor location: lesions were located in the right (3/6) (Fig. 1a-b Case 2), left (2/6) (Fig. 1c-d Case 6), left medial, and right anterior lobe (1/6). Tumor morphology: single multiple cysts were observed in four cases (4/6), while single cysts were observed in two (2/6). The tumor size ranged from 3.4 to 17.0 cm in diameter, with a median diameter of 9.0±6.3 cm. The imaging data of the patients are detailed (Table 1).

Results

Surgical method

All six patients were treated with the surgical operation, which involved resection of the left lateral lobe of the liver; segment Ⅱ+ partial segment V liver resection; laparoscopic fenestration and drainage of liver cyst + cyst wall biopsy; laparoscopic fenestration and drainage of liver cyst + cyst wall biopsy, right hemihepatectomy (open conversion); partial hepatectomy, common bile duct incision, and exploration and T-tube drainage; single-port laparoscopic fenestration and drainage of liver cyst, cyst wall biopsy, then open left hemihepatectomy. The details are shown (Table 2).

Table 2 Operation method, intraoperative condition and follow-up results of 6 cases of IBC

IBC: intrahepatic biliary cystadenoma

Intraoperative Findings And Postoperative Pathology

The tumor was seen intraoperatively as a cystic lesion in all six patients. There were two cases of a single cyst and four of multiple cysts (multicystic with internal segregation). Cystic fluid properties: mucinous cystic fluid was observed in three cases (3/6); brown and turbid cystic fluid in two cases (2/6); while the light yellow clear cystic fluid in one case. The thickness of the capsule wall ranged from 0.1 cm to 0.8 cm. Six patients were pathologically diagnosed with IBC, and in three cases, it was observed that the inner wall of the cyst was covered with a single cubic/columnar epithelium; the cytoplasm was lightly eosinophilic, and the nucleus was located at the base (Fig. 2a-b Case 2). In one case, low-grade neoplasia in part of the covering epithelium was seen under the microscope, and the fibrous connective tissue certificate of the cyst wall was accompanied by hyaline degeneration. In two cases, yellow fat-like deposits were seen in the wall (Fig. 2c Case 6). Pathology showed that the cyst wall was composed of fibrous tissue, covered with a single layer or columnar cubic epithelium, and ovarian-like interstitium was seen locally (Fig. 2d Case 6). The details are shown (Table 2).

Follow-up

All patients in this group were followed up after surgery. The follow-up time was 8-115 months, and the median follow-up time was 28.7±46.2 months. One patient underwent laparoscopic fenestration and drainage of the liver cyst, and intraoperative pathologic biopsy of the cyst wall showed a simple hepatic cyst; the final pathological diagnosis was IBC. The remaining liver volume was too small for the patient to tolerate hepatic resection; therefore, the patient was again referred to our institution after four months with right upper quadrant pain. CT scan revealed extensive nodules in the abdomen, considered malignant transformation, and the patient died three months later. Another patient was diagnosed with recurrent and malignant transformation of IBC 5 years after surgery, and the remaining liver volume was insufficient

Case no.	Operation method	Cystic wall morphology and cyst fluid properties	complication	Follow-up results
1	Resection of left lateral lobe of the liver	Single multicystic mass with wall thickness of 0.1cm, jelly like cystic fluid in the cyst, rough wall, and grayish yellow lipid like deposit in the cyst	no	Alive/115months
2	Segment Ⅷ+ partial segment V liver resection	Single multilocular cystic mass with smooth wall and thickening of 0.1-0.2cm, with jelly like cystic fluid in the cyst	no	Alive/8months
3	Laparoscopic fenestration and drainage of liver cyst + cyst wall biopsy	Single cystic mass, smooth wall, thickening 0.2-0.5cm, brown cystic fluid in the cyst, slightly turbid	no	Died /7 months
4	Laparoscopic fenestration and drainage of liver cyst + cyst wall biopsy, right hemihepatectomy (open conversion)	Single cystic mass, wall thickening, smooth wall, with pale yellow cystic fluid in the cyst	biliary fistula	Alive/28months
5	Partial hepatectomy, common bile duct incision and exploration and T-tube drainage	Single cystic mass with smooth wall and 0.2-0.8cm thickening, with jelly-like cyst fluid in the cyst	biliary fistula	Alive/17months
6	Single-port laparoscopic fenestration and drainage of liver cyst, cyst wall biopsy, then open left hemihepatectomy	Single cystic mass, The wall of the capsule was thickened, 0.2cm, and brown and turbid flocculent liquid was found in the wall, and yellow fat sample deposition was found in the wall	no	Alive/28months

for surgical resection. Following conservative treatment with apatinib, the tumor significantly decreased, and the patient achieved partial response and progression-free survival of 52 months. The patient agreed to continue taking the medication and refused radical surgical resection. The remaining four cases were followed up to date with no recurrence or malignant transformation, and the patients had a good quality of life. Follow-up results are shown (Table 2).

Discussion

Intrahepatic bile duct cystic tumors (IBCTs) are a relatively rare type of cystic tumor of the liver; the etiology of which is still unknown and reported to account for 5% of all intrahepatic cystic diseases[1], With a better understanding of IBCTs and advances in imaging techniques, they are increasingly reported; however, their actual incidence should be higher because they are commonly misdiagnosed as simple liver cysts or other cystic lesions[2]. Most of the lesions are solitary, mostly in the intrahepatic bile ducts and rarely in the extrahepatic bile ducts or the gallbladder[3], and most of the cysts are not identical to the bile ducts. IBCTs can be divided into two histological types: IBC and intrahepatic biliary cystadenocarcinoma (IBCA) [4, 5]. IBC is a precancerous lesion with a malignant rate of up to 30%[2]. Based on the nature of the lining epithelial envelope, they can be classified as mucinous and plasmacythematous and mixed cystadenomas. In 1985, Emer defined cystadenoma of the intrahepatic bile ducts as an intrahepatic multi housed lesion with ovarian-like mesenchymal lining[4]. However, some cystadenoma specimens were not found to have ovarian-like

mesenchyme in clinical practice[6]. Only two of the four female patients with biliary cystadenoma in our group had pathological findings of ovarian-like mesenchyme.

The symptoms and signs of patients with IBC are mostly atypical and related to tumor size and location[7]. When compressing the surrounding tissues or blocking the bile duct, abdominal discomfort or pain may appear, and jaundice may appear when compressing the bile duct. If the tumor ruptures with abdominal or internal bleeding, the patient may show acute abdomen. In a few cases, the combination of bile duct stones, pancreatitis, liver abscess, etc., may show corresponding symptoms. There are no specific tumor markers in the serological diagnosis of this disease, and the main detectors include CA199, CEA, CA125, and AFP. CA19-9 levels are elevated in 60% of patients with IBC and IBCA. Still, it is not specific, and CA19-9 levels are not significantly correlated with the benignity or malignancy of the lesion[8, 9], but CA19-9 levels in serum and cystic fluid are important for IBCA. Levels have some value in the diagnosis of IBCA. In our group, CA125 and AFP levels were not abnormal in the six patients, while the CA19-9 level was elevated in two cases, in addition to CEA in two other cases. In addition to the role of CA19-9 in identifying cystadenoma, CEA was also found to be valuable in the diagnosis of IBC in this group of cases. IBC has a high rate of misdiagnosis. In addition to the lack of specific clinical symptoms and signs, imaging findings are easily confused with cystic liver lesions, such as simple liver cysts, liver abscesses, liver lymphangiomas, IBCA, and hepatic hydatid cyst[10]. Color Doppler ultrasound showed that the sonogram of the bile duct cystadenoma was a round or oval cystic mass in the liver, with a cystic structure, mostly multilocular, with a clear boundary, a complete capsule, and a uniform thin wall. Most of the inner part was an anechoic zone, and there was a separation zone. If the sound transmission in the capsule was poor, the cyst fluid would be thick, the intracapsular septum thickened, wall nodules larger than 1.0 cm, with large calcification; in such conditions, the possibility of IBCA should be considered[11]. On plain CT scan, single or multiple cystic masses could be seen with septation. After contrast enhancement, the wall and septum of the capsule could be enhanced in different degrees. Since the capsule may contain mucus, serous, bile-stained or brown cloud flocculent liquid, or even cholesterol, necrotic or purulent substances, the density of the same capsule or different capsules may be different.

IBC presents as a cystic occupancy on MRI, and the different fluid components within the cyst determine its signal, which is generally a low signal on T1W1 images and a high signal on T2W1 images. Suppose T1W1 high signal is suggestive of hemorrhagic or cystic fluid hyperprotein. In that case, enhancement scans show frequent enhancement of the cyst wall and compartment, with diminished enhancement in the portal vein and equilibrium phase. IBC shows cystic space-occupying lesions on MRI, and the different fluid components in the cyst determine its signal. Generally, T1W1 has a low signal, and T2W1 has a high signal. T1WI images showing a high signal indicate hemorrhagic or high protein in cyst fluid. The enhanced scan showed that the cyst wall and the separation were often enhanced, and the portal vein and balance phase were weakened. MRI has advantages over CT in judging the shape of the cyst contents; in addition, magnetic resonance cholangiopancreatography (MRCP) can show if the cyst is connected to the bile duct, which helps to formulate a surgical plan[11].

MRI has an advantage over CT in determining the shape of the cystic contents, and MRCP can detect if the cyst is communicating with the bile ducts, which can help surgical plans[12, 13]. A significant thickening of the partition, papillary protrusions or wall nodules, gross calcification, or intracystic hemorrhage in the sac indicates hepatobiliary cystadenocarcinoma. In addition, PEC-CT helps exclude IBCA[14, 15]. In imaging diagnosis of suspected IBC or IBCA, trans-invasive examination or percutaneous fine-needle aspiration cytology is not recommended. The fluid component characteristics of the lesion have limited diagnostic value in addition to the risk of the risk dissemination along the needle tract[5]. However, it is easy to misdiagnose a simple hepatic cyst for atypical IBC with smooth wall and no excrescences. In addition, a few cystadenomas may also have cyst wall nodules and calcification; therefore, a high index of suspicion as well close follow-up of atypical patients is necessary to prevent delay in treatment.

As early as 1892, Keen first reported the treatment of IBC by hepatectomy. So far, surgical resection is the first choice for the treatment of IBC[16, 17]. Due to the difficulty of the preoperative diagnosis of IBC and the high rate of malignant transformation, it is recommended that a possible diagnosis of IBC be considered in all patients with atypical hepatic cystic diseases. Since the disease is prone to recurrence, the rate of postoperative recurrence in treatment methods, such as fenestration drainage and tumor enucleation exceeds 90%[][7]; thus, the above treatment methods can't achieve a radical cure. For any suspected IBC to be completely removed, regular hepatic lobectomy should be performed as far as possible to ensure complete resection of the cyst wall and reduction of the recurrence rate[18]. Liver transplantation may be considered in cases where the disease involves the whole liver or incomplete enucleation[19] .For IBC inappropriately treated with fenestration drainage; surgery should be performed as early as possible after functional evaluation. Unfortunately, up to now, a small number of doctors still have an insufficient understanding of IBC. IBC mistakenly underwent fenestration and drainage according to the hepatic cyst, resulting in adverse consequences for patients.

Observing this group of cases found that for patients with IBC, if the cyst wall is thickened during operation, especially for cyst wall with yellow vegetations, the cyst fluid is turbid and flocculent, or a viscous liquid, accompanied by bile-like or dark red bloody fluid, or the shape of the polycystic liver cyst fluid is different, we highly suspect IBC. So, we recommend paying attention to cystic wall morphology and cyst fluid properties during the operation. At the same time, it is recommended that patients diagnosed with liver cysts undergo intraoperative pathological diagnosis and strengthen communication with pathologists to deepen understanding of IBC. It is recommended to perform multiple pathological biopsies or direct liver resection to avoid missing adverse lesions and the possibility of reoperation [19]. Besides, intraoperative pathologic diagnosis is recommended routinely for all liver cyst operations. Owing to the recurrence of IBC, it is recommended that patients undergo examination regularly after the operation. Patients with recurrence can be operated actively, and advanced cases with recurrence and malignant transformation should be treated with radiotherapy, chemotherapy, TKI drugs, or hyperthermic perfusion, which is beneficial in alleviating terminal symptoms[20–22].

Conclusion

IBC is a rare cystic tumor of the liver. It has no specific clinical symptoms and signs. Single-cystic hepatobiliary cystadenoma has a very high rate of missed diagnosis and misdiagnosis, requiring a fine clinical acumen. We recommend paying attention to cystic wall morphology and cyst fluid properties during the operation. At the same time, it is recommended that all patients diagnosed with liver cysts undergo intraoperative pathological diagnosis and strengthen communication with pathologists to deepen understanding of IBC, improve the level of rapid pathological diagnosis, and reduce the rate of misdiagnosis, misoperation, and even secondary operations.

Abbreviations

MRI: Magnetic resonance imaging; CT: Computed Tomography; CEUS: contrast-enhanced ultrasonography; MRCP: magnetic resonance cholangiopancreatography; IBC: intrahepatic biliary cystadenoma; IBCA: intrahepatic biliary cystadenocarcinoma; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; AFP: alpha fetoprotein; CA 125: carbohydrate antigen 125; HE: hematoxylin-eosin.

Declarations

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Authors' contributions

All authors read and approved the final manuscript. YYG and LMY performed the surgery. CWH and LZB wrote the original draft. DXQ and WYJ collected and arranged imaging and pathological data. LLJ and YYG designed the study and revised the manuscript.

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Availability of data and materials

All the data and materials are from the laboratory tests and examinations of patients in the Affiliated Hospital of Guangdong Medical University, and can be obtained from the corresponding author upon reasonable request.

Ethics approval and consent to participate

All methods were performed in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Affiliated Hospital of Guangdong Medical University.

The need for informed consent was waived by The Ethics Committee of Affiliated Hospital of Guangdong Medical University.

Consent for publication

Written informed consent was obtained from the patients or their relatives for the publication of this study.

Competing interests

The authors declare that they have no competing interests.

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Figures

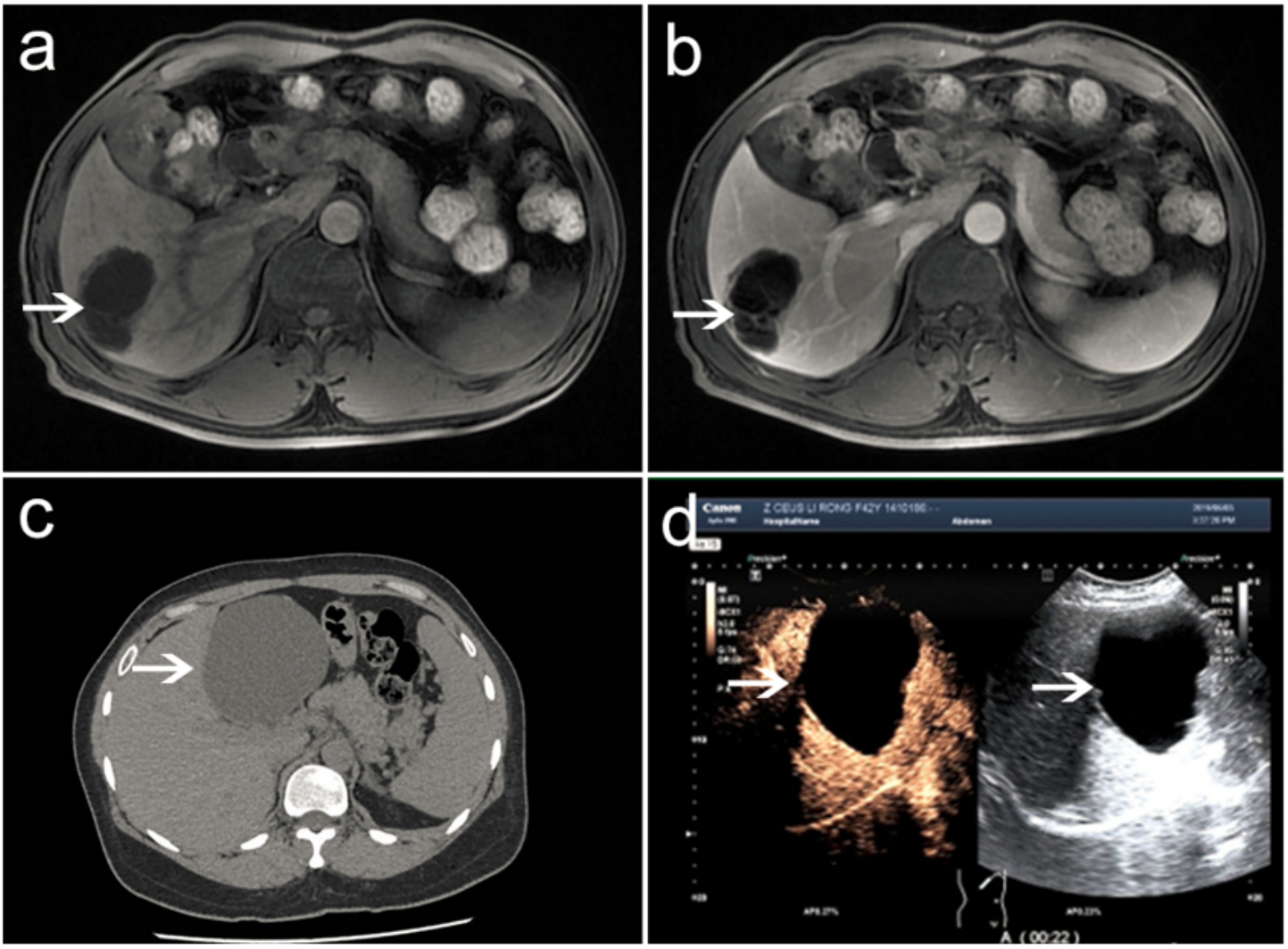

Figure 1

MRI examination (Case 2). Cystic mass in the right lobe of the liver, showing multilocular cystic changes (shown by white arrow) (a). Contrast-enhanced T1-weighted images showed that the cyst wall was separated and enhanced, and there was no nodule on the cyst wall, and the contents of the lesion were not enhanced in portal vein phase(b) CT examination (Case 6). A round low-density shadow is seen in the left lobe of the liver, with clear edges and uniform density in the capsule(c). Contrast-enhanced liver ultrasound showed cystic space occupying the left outer lobe of the liver, with clear borders, good sound penetration in the cyst, and floating sheet echoes in the local area. There was no enhancement in the cysts at various stages after injection of contrast agent(d)

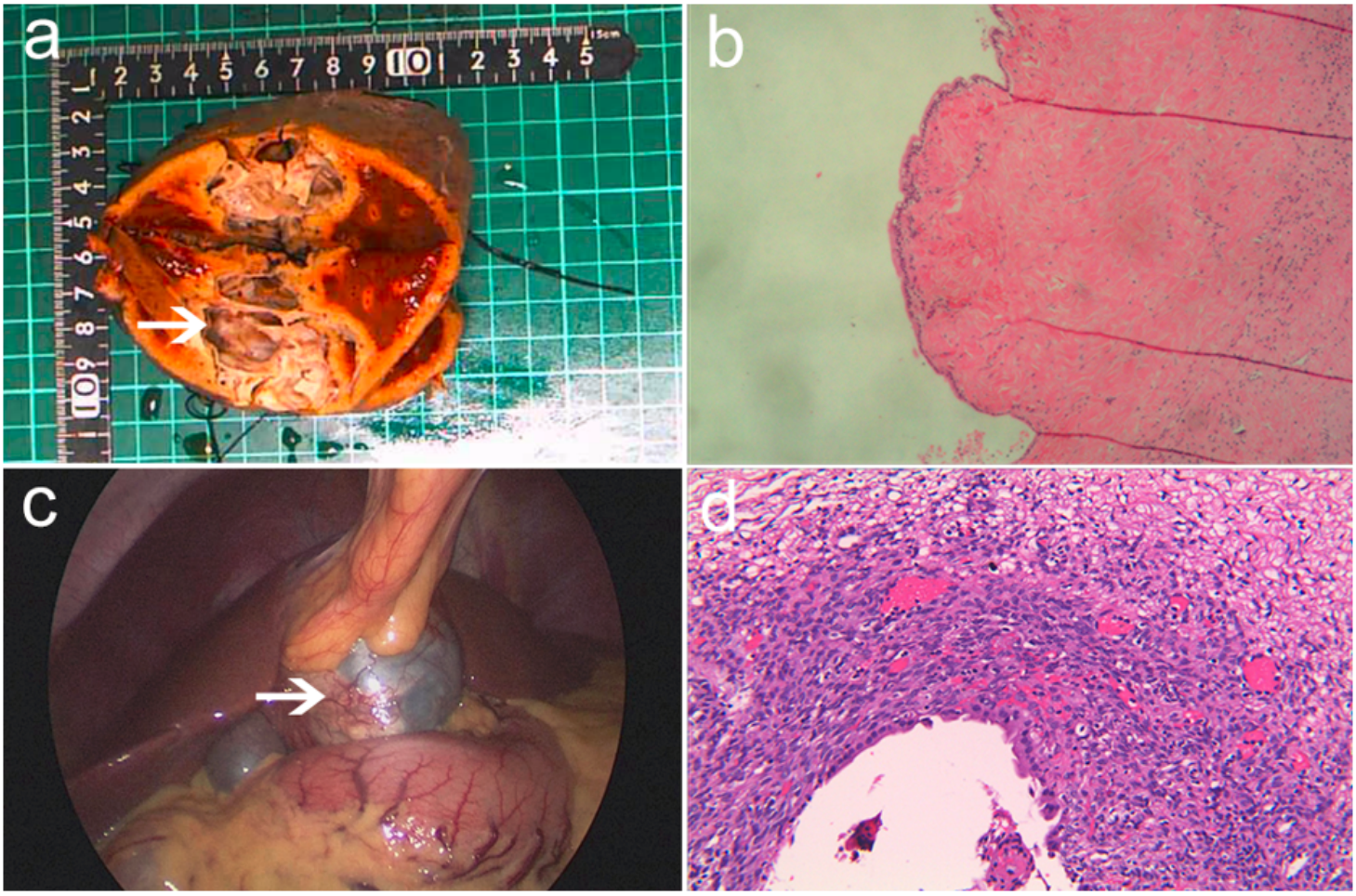

Figure 2

Tumor shape (intraoperative/postoperative) and postoperative pathology. Case 2. The resected specimen showed cystic and multilocular masses with jelly-like cystic fluid(white arrow), with a wall thickness of 0.1-0.2cm and smooth inner wall (a). Under the microscope, the inner wall of the cyst was covered with a single layer of cuboidal/columnar epithelium, with eosinophilic cytoplasm and nucleus at the base (HE 200 ×) (b) Case 6. Laparoscopic exploration revealed yellow fat-like deposits in the cyst wall (white arrow) and turbid brown cyst fluid (c). Under the microscope, the cyst wall was composed of fibrous tissue, covered with monolayer or columnar, cuboidal epithelium, and ovarian-like stroma was seen locally(d)