Case Reports in Gastroenterology

Case Rep Gastroenterol 2022;16:535–545
DOI: 10.1159/000526196
Received: March 17, 2022
Accepted: June 17, 2022
Published online: August 31, 2022

Single Case

Atypical Biliary Adenofibroma of the Liver: Related Treatment and Performance

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Keywords

Biliary adenofibroma · Benign liver tumor · Cholangiocarcinoma · Malignant transformation · Precancerous lesions

Abstract

Biliary adenofibroma is an extremely rare benign liver tumor, but it may be a precancerous lesion of cholangiocarcinoma. So far, only 29 cases have been reported in the literature. A 30-year-old woman was admitted to our department for upper abdomen mass. The computed tomography scan showed a huge cystic and partly substantial mass between the left lobe of the liver and the descending duodenum, which was considered to be an exophytic tumor derived from the left lobe of the liver. Laparoscopic liver segment IVb resection and cholecystectomy were performed. Microscopic examination showed that the tumor was composed of glandular cavities of varying sizes and fibrous interstitium. The glandular cavity was covered with cubic or columnar epithelium without atypia. Some of the mesenchymal cells are myofibroblast-like and spindle-shaped with red-stained cytoplasm. The mesenchymal cells in some areas proliferate densely with moderate atypia. It was considered to be an atypical biliary adenofibroma with focal necrosis and active cell proliferation which may have malignant transformation potential. There was no recurrence and metastasis at a 6-month follow-up. Biliary adenofibroma is a rare benign tumor derived from the bile duct, but it may progress to malignancy and develop distant metastasis. It is difficult to distinguish it from other liver tumors through imaging examination and the gold standard of diagnosis is histopathological examination. Close clinical follow-up is recommended.

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DOI: 10.1159/000526196

Introduction

According to 2019 WHO tumor classification system, biliary adenofibroma (BAF) is classified as a benign biliary tumor. Tsui et al. [1] first reported it in 1993. So far, less than 30 cases have been reported in English literature, and 16 of them have malignant transformation (Table 1). According to 29 case reports that have been published, the patient had no specific symptoms. Most of the patients were diagnosed unexpectedly during examination or referred to hospital because of abdominal pain or palpable mass. A minority of patients presented with postprandial nausea, vomiting, fever, jaundice, and itching. Male and female patients were divided with roughly the same size. Patients were aged from 21 to 79 years old and the tumor size ranged from 2 to 25 cm. The imaging study generally detected a low-density shadow with clear border, uneven density, uneven enhancement, as well as edema zone surrounding and necrosis in the center. Imaging was not specific for the diagnosis of BAF, so the diagnosis of BAF depended on pathological examination. Histology was characterized by hyperplastic ducts, acini, and microcystic dilated bile ducts embedded in abundant fibroblastic stroma, lining cubic or low columnar epithelium (nonmucus-secretory type). Cytoplasm showed double colors and nucleus was round or oval with small nucleoli but without atypia. This article reports a case of BAF and reviewed the literature to explore its clinical symptoms, pathological features, imaging findings, as well as differential diagnosis and prognosis, to improve the understanding of the disease.

Case Presentation

A 30-year-old woman was admitted to our department on June 22, 2020, for an upper abdominal mass. The patient had no obvious discomfort. The texture of the mass was slightly hard and the border was clear. The patient had no history of hepatitis B virus infection and the tests for other hepatitis virus were negative. It was worth noticing that the patient gave birth on April 23rd, but no liver lesion was found during the birth examination by ultrasonography, which meant that the mass grew fast. However, the patient's pregnancy proceeded smoothly with no special medication used. The patient did not smoke and there was no other related surgical history or family history. The liver function of patient was normal. For differential diagnosis of hepatocellular carcinoma and liver metastases from other gastrointestinal tumors, we performed the detection of common tumor antigens. The concentration of alpha-fetoprotein (AFP) was within the normal range while that of carbohydrate antigen 19-9 (CA 19-9) was slightly elevated (42.5 U/mL). The abdominal computed tomography (CT) scan showed that the mass between the left inner lobe of the liver and the descending segment of the duodenum was considered as an exophytic tumor derived from the left outer lobe of the liver, with a size of 98 mm × 81 mm × 71 mm. Several slightly swollen lymph nodes were in the right heart phrenic angle area and hepatic hilar area (Fig. 1). The abdominal magnetic resonance imaging (MRI) dynamic scan showed exophytic tumor derived from the left inner lobe of the liver. It was possible that the tumor was derived from mesenchymal tissues. Primovist is a gadoxetic acid disodium injection. The signal of normal liver cells increases in MRI after uptake of the contrast agent, while the diseased cells no longer take up the contrast agent and the signal decreases. The uptake of Primovist of the liver parenchyma of the tumor was reduced, which meant that the function of these liver cells was impaired (Fig. 2).

Laparoscopic liver segment IVb resection and cholecystectomy were performed on June 28, 2020. During the operation, a tumor was seen on the liver segment IVb. The size of the soft tumor was about 9 × 8 cm and it had a clear border. The duodenum and transverse colon were

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Table 1. Clinical data of BAF in 29 patients previously reported in the literature

No.	Reference	Age/sex	Tumor size, cm	P53	Ki67, %	Malignant transformation	Mutations found	Follow-up
1	Tsui et al. [1]	74/f	7			No		No recurrence after 2 years
2	Parade et al. [2]	49/f	7			No	Abnormality of chromosome 22	No recurrence or metastasis
3	Haberal et al. [3]	21/m*	20					No recurrence at 2-year follow-up
4	Akin and Coskun [4]	25/m*	14 in liver; 2.5 in lung			Pulmonary metastasis		Developed local recurrence and pulmonary metastasis at 3-year follow-up
5	Garduno-Lòpez et al. [5]	68/f	6			No		No recurrence at 30-month follow-up
6	Varnholt et al. [6]	47/f	16	Positive		No	Tetraploidy status with a low S-phase	No recurrence at 3-year follow-up
7	Menegazzo et al. [7]	79/m				No		
8	Gurrera et al. [8]	79/m	5.5	Negative	1	No		No recurrence at 7-year follow-up
9	Kai et al. [9]	40/m	7	Negative	5–10	Atypia		No recurrence at 8-month follow-up, died of fulminant hepatitis B
10	Nguyen et al. [10]	53/f	6.5			Yes		No recurrence at 12-month follow-up
11	Tsutsu et al. [11]	69/f	3.5	Focally positive	10–15	Yes		No recurrence at 4-year follow-up
12	Jacobs et al. [12]	57/f	10			Atypia		No recurrence at 5-year follow-up
13	Thai et al. [13]	77/m	4.8			Yes		
14	Elpek et al. [14]	23/m	6			No		
15	Godambe et al. [15]	71/f	5.7	25–50%	50	Yes		
16	Thompson et al. [16]	71/m	14.5			Yes		No recurrence or metastasis of liver tumor but patient died 9 years later from a new primary lung malignancy
17		71/m	6.3			Yes	Nonsense mutation in the tumor suppressor protein $p16^{INK4a}$ encoded by CDKN2A	No recurrence or metastasis at 1-month follow-up
18	Kaminsky et al. [17]	37/f	4.5	Negative	50	Yes		No recurrence after 4 months
19	Arnason et al. [18]	83/m	7		60			Not resected, alive with tumor at 14 months
20		47/f	16		6	Atypia	Large region gains in chromosome 1q; loss of 1p, 2p, 3q, 6q, 8p, 11p, 12q, 14, 16q	Recurred 6 years later, liver transplant at 7 years, died at 7.5 years due to transplant complications

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Table 1 (continued)

No.	Reference	Age/sex	Tumor size, cm	P53	Ki67, %	Malignant transformation	Mutations found	Follow-up
21		57/f	10; 2.5; 1.7	Positive	≤10	Atypia	Gain of 1q; loss of 11q, 22q, Xq; focal amplifications of CCND1 and ERBB2	No recurrence at 3 years
22		70/f	12	Negative	≤8	Atypia	Gain of 1q, 4p, 5, 8, 12p; losses of 1p, 4q,6q, 11p, 14q, 17p	Recurred 12 months postoperatively with 6 cm mass, had hepatic arterial embolization
23		74/f	7	Negative	2	No	No chromosomal changes	No recurrence in 20 years, died of unrelated disease at age 94
24		46/m	15	Patchy positive	<1	Atypia		Alive with no recurrence in 21 years
25	Esteban et al. [19]	26/f	2.6			No		No recurrence or metastasis after 3 months
26	Chua et al. [20]	66/f	2	Positive	2 (BAF); 30 (CC)	Yes; cholangiocarcinoma		No recurrence at 6 weeks, accepted adjuvant chemotherapy
27	Sturm et al. [21]	63/f	6.5	Focally positive	20–30	Yes	TP53 and KIT (NM_000546.5: c.215C>G, TP53; NM_000222.2: c.1621A>C, KIT)	No recurrence or metastasis after 24 months
28	Lee et al. [22]	63/m	4.7	Focally positive	<2	No		No recurrence or metastasis after 41 months
29		38/m	2.7			No		No recurrence or metastasis after 39 months

*Considering the rarity of the disease, the clinical history of 2 patients, and the timing of case reports, we inferred that 2 patients were the same person.

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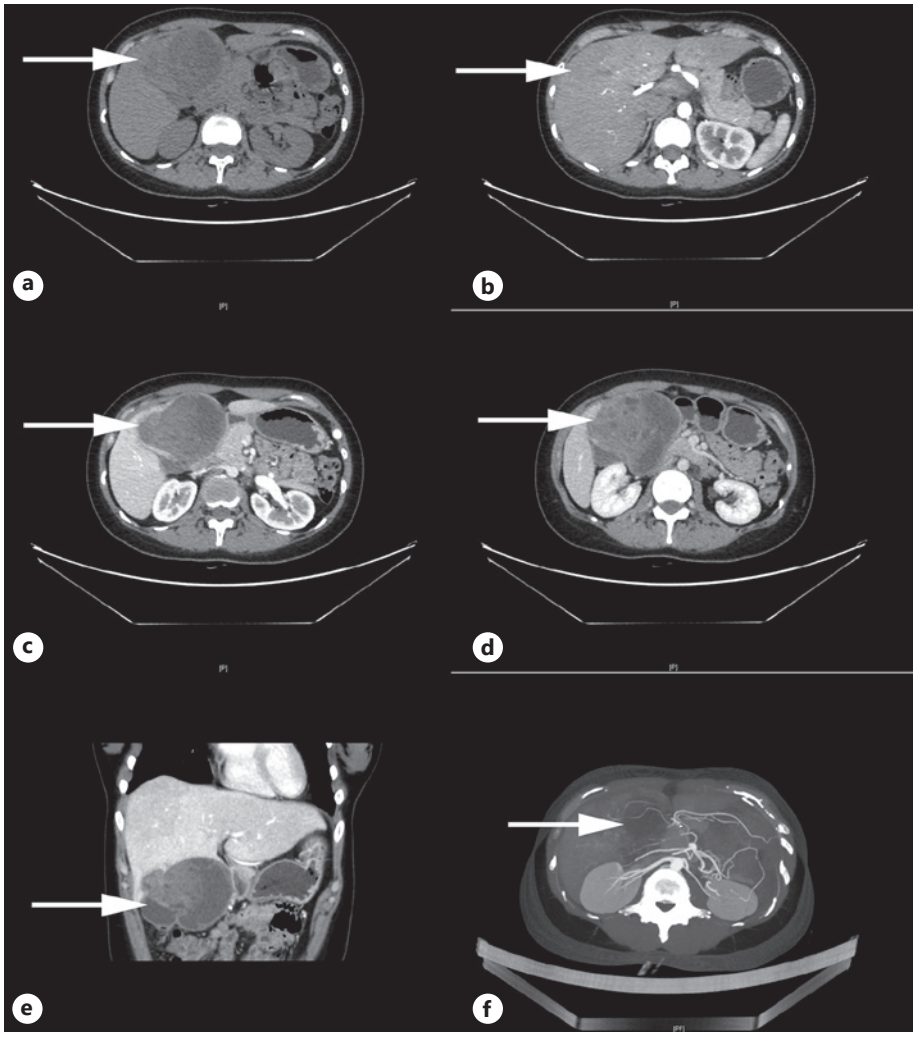

Fig. 1. CT imaging of BAF. CT imaging features of BAF in the liver of a 30-year-old female patient. **a** Medium. **b** Arterial phase. **c** Venous phase. **d** Portal phase. **e** Coronal plane image. **f** Processed image. The CT scan showed a low-density mass (98 mm × 81 mm × 71 mm) between the left inner lobe of the liver and the descending segment of the duodenum. The mass was uneven with cystic portion and solid parenchyma. The lesion and the left inner lobe of the liver were not clearly demarcated, and the adjacent gallbladder, duodenum, and pancreas were significantly compressed (**e**). The mass showed strip-like enhancement in the arterial phase and low enhancement in venous and delayed phase (**b–d**). The upper abdominal CTA showed that the blood supply came from the left inter-hepatic artery and its branches, and the right renal artery and vein was compressed (**b**, **f**).

obviously oppressed. We resected the liver parenchyma within 2 cm from the tumor edge. There was no recurrence or metastasis in the 6-month follow-up.

The excised liver tissue was about 11 cm × 9 cm × 8 cm. A gray-yellow mass could be seen on the cut surface of the specimen, with a volume of 8.5 cm × 7.5 cm × 7 cm. The soft tumor was cystic, partly substantial, with an unclear border (Fig. 3). The tumor was closely adjacent to the liver capsule and it was about 1.2 cm from the nearest liver cut edge. The rest of the liver cut surface was gray-red, solid, soft.

The tumor was composed of glandular cavities of varying sizes and fibrous mesenchyme with sheet-like hyperplasia. The glandular cavity was covered with cubic or columnar

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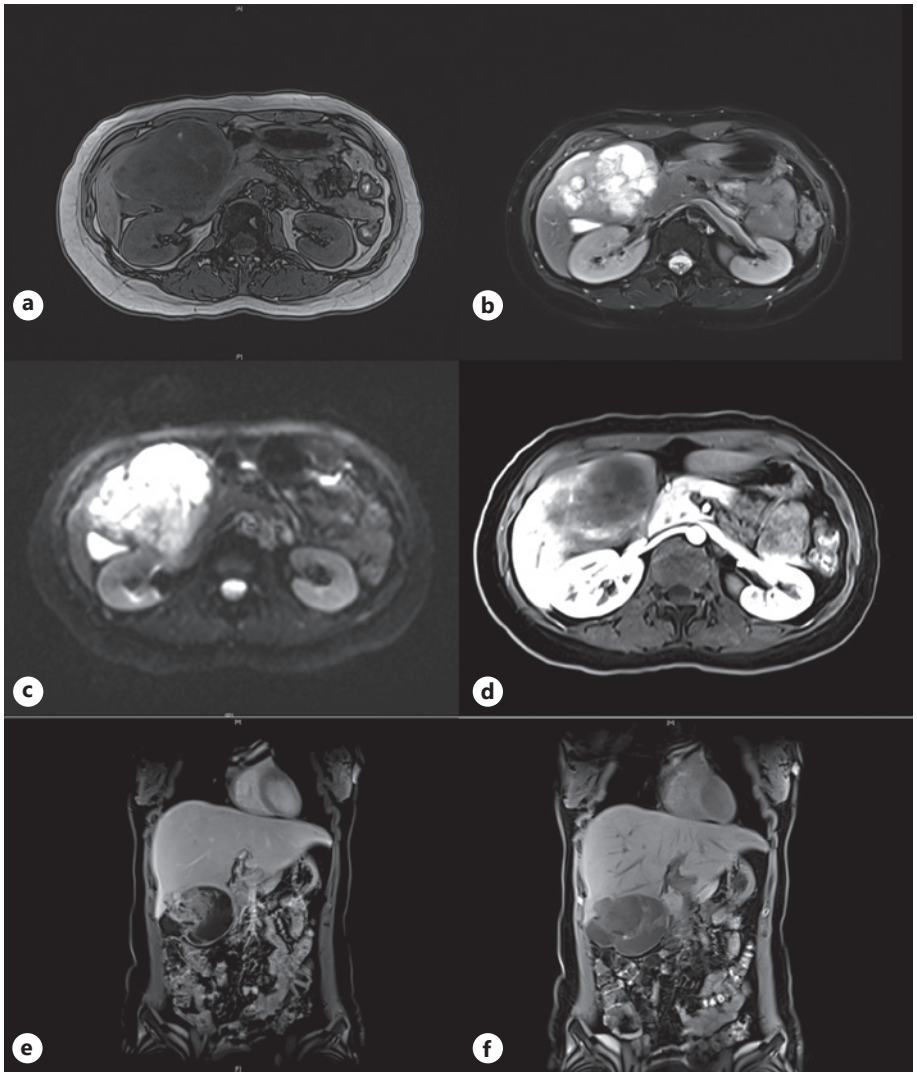

Fig. 2. MR imaging of BAF. MR imaging features of BAF in the liver of the patient. **a** T1-weighted image. **b** T2-weighted image. **c** Diffusion-weighted imaging (DWI). **d** Dynamic contrast-enhanced MR imaging. **e**, **f** Coronal plane images. A lobular mass (98 mm × 81 mm × 71 mm) could be seen between the lower edge of the left inner lobe of the liver and the descending segment of the duodenum, which was cystic and partly solid with obvious uneven signal. T1WI showed low/equal/slightly high confounding signal (**a**). T2WI showed slightly higher/high confounding signal. Separation showed slightly lower signal (**b**). On DWI, the solid part showed limited dispersion (**c**). The enhanced scan shows progressive enhancement in the solid component while no enhancement was seen in cystic part. No contrast agent uptake could be seen in the hepatobiliary stage. The uptake in the left inner hepatic lobe was reduced and there was no clear boundary between the lesion and the left inner lobe in the hepatobiliary stage (**f**, white arrow).

epithelium. There was no obvious atypia. The mesenchymal cells were spindle-shaped and partially myofibroblast-like with red-stained cytoplasm. In some areas, the mesenchymal cells proliferated densely with moderate atypia. Some tissue cells showed hyperplasia with infiltration of more lymphocytes, plasma cells as well as neutrophil, and sediment of hemosiderin. It was considered as atypical BAF with focal necrosis and active cell proliferation which may have malignant transformation potential (Fig. 3). Close clinical follow-up was recommended. The tumor invaded the liver capsule, but no clear intravascular tumor thrombus

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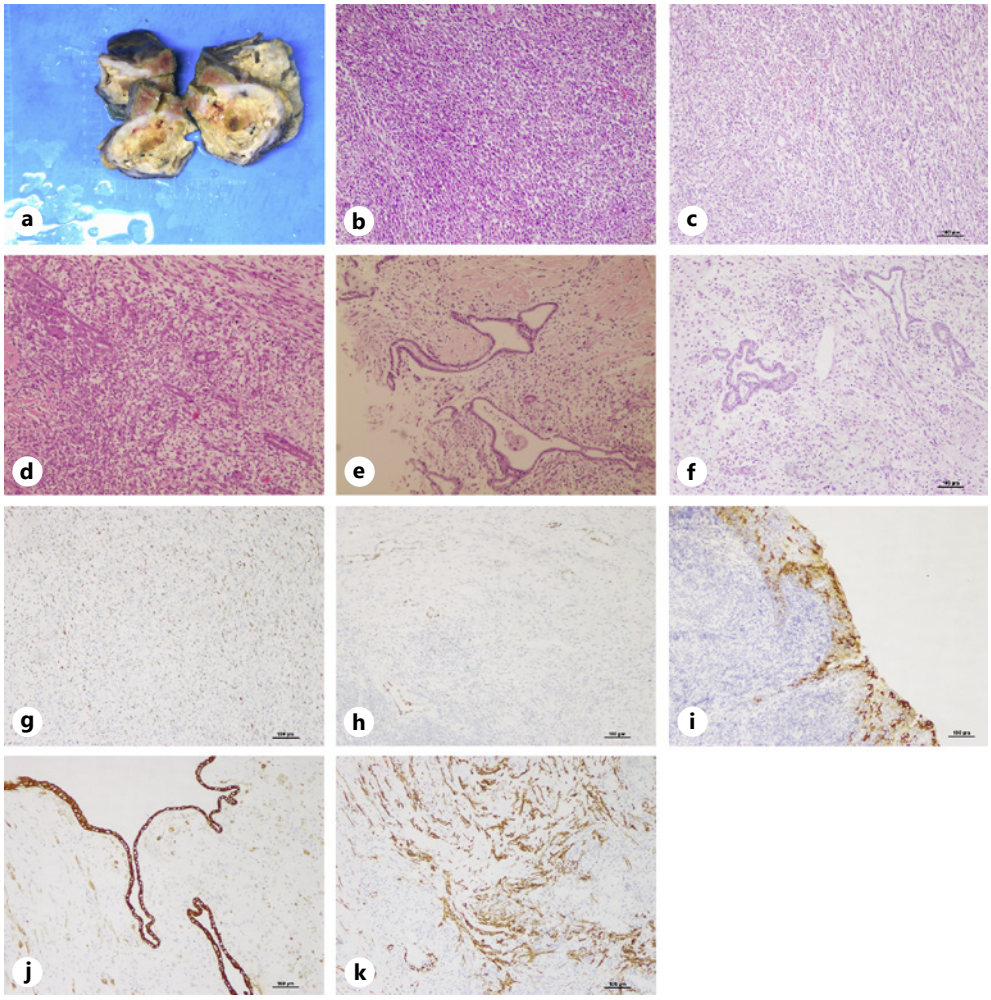

Fig. 3. Histopathological examination of BAF. Histopathological examination of BAF of the patient. The excised liver tissue was about 11 cm × 9 cm × 8 cm. A gray-yellow mass could be seen on the cut surface of the specimen, with a volume of 8.5 cm × 7.5 cm × 7 cm. The soft tumor was cystic, partly substantial, with an unclear border (**a**). Some tissue cells showed hyperplasia with infiltration of more lymphocytes, plasma cells as well as neutrophil, and sediment of hemosiderin (**b**, **c**, H&E. ×10). The tumor was composed of glandular cavities of varying sizes and fibrous mesenchyme with sheet-like hyperplasia. The glandular cavity was covered with cubic or columnar epithelium (**d–f**, H&E. ×10). Immunohistochemistry p53 showed positive expression in mesenchymal component and epithelial component, while the expression of mesenchymal component was more abundant (**g**, **h**, ×10). Epithelial cells were positive for CK7 (**i**, ×10). Positive immunostaining for CK8 was observed in the epithelial component (**j**, ×10). Positive immunostaining for α-smooth muscle actin was observed in the fibrous stroma (**k**, ×10).

was seen and tumor cells could not be seen at the edge of the specimen. Special staining: Masson's tricolor showed that the staging of liver fibrosis was S2. Immunohistochemistry showed slice 1: epithelial component: CD31 (−), CD34 (−), ERG (−), CK (−), nonepithelial component: vimentin (+), TFE-3 (+), FLi-1 (+), actin minority (+), S-100 minority (+), P53 about 40% (+), Ki67 hot spot area about 10% (+), desmin (−), ALK (−); slice 2: epithelial component: SMMHC part (+), CK part (+), CK7 minority (+), CK8/18 minority (+), P63 minority (+), B-catenin (+) in membrane, nonepithelial component: INI-1 (+), CD68 (+), HHF35 part (+), SOX 10 partial weakly (+), CD23 minority (+), CD30 minority (+), MyoD1 (−), myogenin (−), CD21 (−), HMB45 (−), melan A (−); in situ hybridization: EBers (−). The results of

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immunohistochemistry showed that its ability to multiply was weak. There were epithelial components in tumor and there might be components derived from smooth muscle. The rapidly grew tumor might relate to the hormone status during pregnancy. The patient recovered smoothly and was discharged 9 days after the operation.

Discussion

Benign bile duct tumors are relatively rare, including BAF, bile duct adenoma, bile duct hamartoma (von Meyenburg complexes), bile duct cyst adenoma, and so on. So far, there are only 29 cases of BAF reported in literature, including 14 males and 15 females, aged from 21 to 79 years old and the tumor size ranged from 2 to 25 cm (Table 1). The imaging study generally detects a low-density shadow with clear border, uneven density, uneven enhancement, as well as edema zone surrounding and necrosis in the center. The MRI features usually reveal a well-circumscribed multiseptated multicystic tumor that varies in diameter. The tumor exhibits hypointensity on the precontrast T1-weighted image and hyperintensity on the T2-weighted image. After contrast administration, septa and wall enhancement are noted. There is no communication with the bile ducts on MRI [22].

However, imaging is not specific for the diagnosis of BAF, so the diagnosis of BAF still depends on pathological examination. The large BAF can reach 20 cm in diameter (Table 1), with clear boundary and no capsule. The center of the tumor can have a round or oval thin-walled cyst with a diameter of 1~5 mm, which is a small bile duct with cystic expansion. Other area of the tumor is a dense interstitium without necrosis. Histology is characterized by hyperplastic ducts, acini, and microcystic dilated bile ducts embedded in abundant fibroblastic stroma, lining cubic or low columnar epithelium (nonmucus-secretory type). Cytoplasm shows double colors and nucleus is round or oval with small nucleoli but without atypia [1]. The bile duct epithelium-related keratin markers are positive and mucus staining is negative.

The abovementioned benign bile duct tumors were found in peripheral cholangiocarcinoma, which means that these lesions may be related to peripheral cholangiocarcinoma [13]. At present, there is no uniform standard for malignant transformation of BAF. We summarize the literature in Table 1 into following aspects: (a) Dysplastic and papillary epithelial changes: epithelial cells grow papillae into the cavity (especially microcystic structure), which can be a complex papillary structure with fibrovascular axis. The arrangement of epithelial cells is pseudo-barrier-like and the cells are crowded. Glands are cribriforming or back-to-back structure type. (b) The epithelial cells are columnar with increased layers, polar disorder, and mild to severe atypia. The nuclei are long, vesicular, and deeply stained with atypia and prominent nucleoli. The cytoplasm shows eosinophilic, apocrine secretion-like changes and secretory vesicles. Mitotic figures can be seen. (c) Single atypical cell or abnormal duct structure with incomplete structure is seen in the interstitium. The tumor invades the liver capsule, nerves, vessels, and tissues around the liver, all of which indicate infiltration. (d) Cholangiocarcinoma coexists with classic BAF and atypical BAF.

In 1997, Parada et al. [2] found that there was an abnormality of chromosome 22 in BAF by fluorescence in situ hybridization. This abnormality is common in benign mesenchymal tumors, especially in meningiomas and schwannomas, but rare in sarcomas and epithelial tumors. In 2017, Arnason et al. [18] used array comparative genomic hybridization to analyze tumor DNA and identified losses in 22q in 1 of the 3 cases tested. The finding of multiple clonal cytogenetic alterations by array comparative genomic hybridization in the 3 cases that tested successfully provides further genetic support to the hypothesis that BAFs are indeed neoplastic lesions. The amplifications of CCND1 and ERBB2 that were detected are not typical of benign

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neoplasms and are genetic changes that suggest that the tumors may have the ability to behave aggressively. Indeed, ERBB2 amplification occurs frequently in cholangiocarcinoma [23].

Thompson et al. [16] used second-generation sequencing technology to find that, in malignant BAF (BAF with cholangiocarcinoma), the tumor suppressor protein p16 encoded by the CDKN2A gene had a nonsense mutation, suggesting that it may be related to the malignant transformation of BAF. The CDKN2A mutation identified has previously been implicated in the pathogenesis of biliary dysplasia and cholangiocarcinoma [24].

Although the origin of BAF is unknown, the epithelial expression of D10, yet without 1F6, observed in Varnholt's case may suggest an origin similar to bile duct hamartoma [6]. In previous cases, authors observed that BAF may be accompanied by mild to severe atypical hyperplasia of epithelial components, carcinoma in situ, and even infiltration of the tumor. But in our case, we did find that the mesenchymal cells were spindle-shaped and partially myofibroblast-like with red stained cytoplasm. In some areas, the mesenchymal cells proliferated densely with moderate atypia. Some tissue cells showed hyperplasia with infiltration of more lymphocytes, plasma cells as well as neutrophil, and sediment of hemosiderin. The cells proliferated actively with focal necrosis, which may have malignant transformation potential. Therefore, it is inferred that BAF can be malignant transformation of epithelial component and mesenchymal component.

CA 19-9 is a serum marker normally synthesized by pancreatic and biliary epithelium, and it is known to be slightly elevated in benign biliary and pancreatic disease [25]. Garduno-Lòpez et al. [5] reported a case that described of BAF producing high levels of CA 19-9.

Of note, intermediate stages of cystic biliary proliferation resembling bile duct hamartomas and BAFs have been reported in an animal model of aflatoxin-induced cholangiocarcinoma [26]. The above experimental findings, along with the large size, the p53 expression, and the tetraploidy status with a low S-phase being occasionally reported strongly suggest that BAF could represent a premalignant lesion [6].

BAF is a benign lesion, but it has a tendency to become malignant. BAF needs to be differentiated from other benign bile duct tumors, such as bile duct hamartoma (von Meyenburg complex), bile duct adenoma, bile duct cystadenoma, and so on. In addition, it is difficult to confirm the diagnosis by preoperative imaging examination. Therefore, surgeon should completely resect the lesion and surrounding normal liver tissue. The patients confirmed by postoperative pathology examination that there is no sign of malignant changes that can be cured. There are 16 cases with malignant transformation reported in the literature. One case relapsed with lung metastasis after 3 years follow-up. The other 2 cases of relapse were treated with hepatic arterial embolization and liver transplantation. The latter died after 7.5 years from the diagnosis due to transplant complications. Eleven cases were followed up without recurrence. In this case, the patient grew a huge liver mass within a few months, with no obvious discomfort, in a few months after her pregnancy. The tumor that grew rapidly may be related to the hormone status during pregnancy, but to prove this assumption we need more clinical evidence. Postoperative pathology examination showed that most of the tumor was atypical BAF, with some mesenchymal cells being moderately atypia. No recurrence was found after 6 months of follow-up.

In summary, classic BAF is a benign lesion, but it has a tendency to progress to malignancy. BAF may be a kind of peripheral cholangiocarcinoma precursor lesions, which manifests as a progressive change in epithelial or mesenchymal components from atypical hyperplasia to cancer or even metastasis. Due to the minority of articles of BAF and the fact that most of them are case reports, as well as the lack of systematic and in-depth research, the evidence for whether BAF is a precancerous lesion of cholangiocarcinoma is still insufficient. Detailed histopathological examination of the tumor is the key to diagnosis.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

This work was supported by the Natural Science Foundation of China (82173229) and the Guangdong Basic and Applied Basic Research Foundation (2021A1515010095).

Author Contributions

Shao-Ru Liu and Ming-Bin Feng conceived the case report. Shao-Ru Liu and Qing Yan were the major contributors to the writing of the manuscript. Shao-Ru Liu, Qi Zhu, Tai-Feng Zhu, and Lei-Bo Xu were the major contributors to critical revision of the manuscript for important intellectual content. Lei-Bo Xu provided expert opinion and final approval of the version to be published.

Data Availability Statement

All authors read and approved the final manuscript. All the generated data are included in this article. Further inquiries can be directed to the corresponding author.

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