Case Report

Malignant transformation of biliary adenofibroma: a rare biliary cystic tumor

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Abstract: Biliary adenofibromas (BAFs) are rare, benign biliary cystic tumors with potential for malignant transformation. Of the eleven prior cases of BAF reported in the literature, six showed evidence of malignant transformation. We describe the clinical, imaging and pathology features of two cases of malignant BAF and review the existing literature to raise awareness of this entity and provide additional tools for diagnosing this rare tumor Additionally, we identified a loss of function mutation in the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) tumor suppressor gene in a malignant caudate lobe BAF, thereby providing potential insight into the molecular pathogenesis of BAF malignant transformation. Although additional cases and longer-term follow-up are needed, our cases suggest that recurrence or metastasis of malignant BAF is not common and that complete surgical resection can be curative.

Keywords: Biliary adenofibroma (BAF); malignant transformation; caudate lobe; tumor suppressor; next generation sequencing

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Introduction

Biliary adenofibromas (BAFs) are rare, benign biliary cystic tumors with uncommon potential for malignant transformation (1,2). To our knowledge, only 11 cases of BAF have been reported in the literature (1-12). We performed a database search to find cases of BAF diagnosed at Mayo Clinic from years 1994 to 2016. We describe two cases of malignant BAF.

Case presentation

Case 1

A 71-year-old male was referred to a hepatologist for evaluation of a large mass in the left lateral hepatic lobe, discovered incidentally during screening ultrasound (US) for an abdominal aortic aneurysm (AAA). At the time of evaluation, the patient denied weight loss, fever, chills or jaundice. The patient was a chronic smoker and consumed two drinks per day. The remaining past medical, surgical, family and social history were non-contributory. The patient was obese with a body mass index (BMI) of 38.8 kg/m^2 with an otherwise unremarkable physical examination; there were no stigmata of chronic liver disease. Tumor markers including AFP and CA 19-9 were not elevated. Liver function tests were within normal limits and serology was negative for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Magnetic resonance imaging (MRI) was performed, which showed a 14.5 cm × 10 cm × 6.3 cm complex mass with both solid and cystic components confined to the left hepatic lobe (*Figure 1*). There were two enlarged periportal lymph nodes measuring 1 cm concerning for metastasis (not shown). The remainder of the liver had a normal morphologic appearance. Staging studies including a PET/CT scan (positron emission tomography/computed tomography) and esophagogastroduodenoscopy

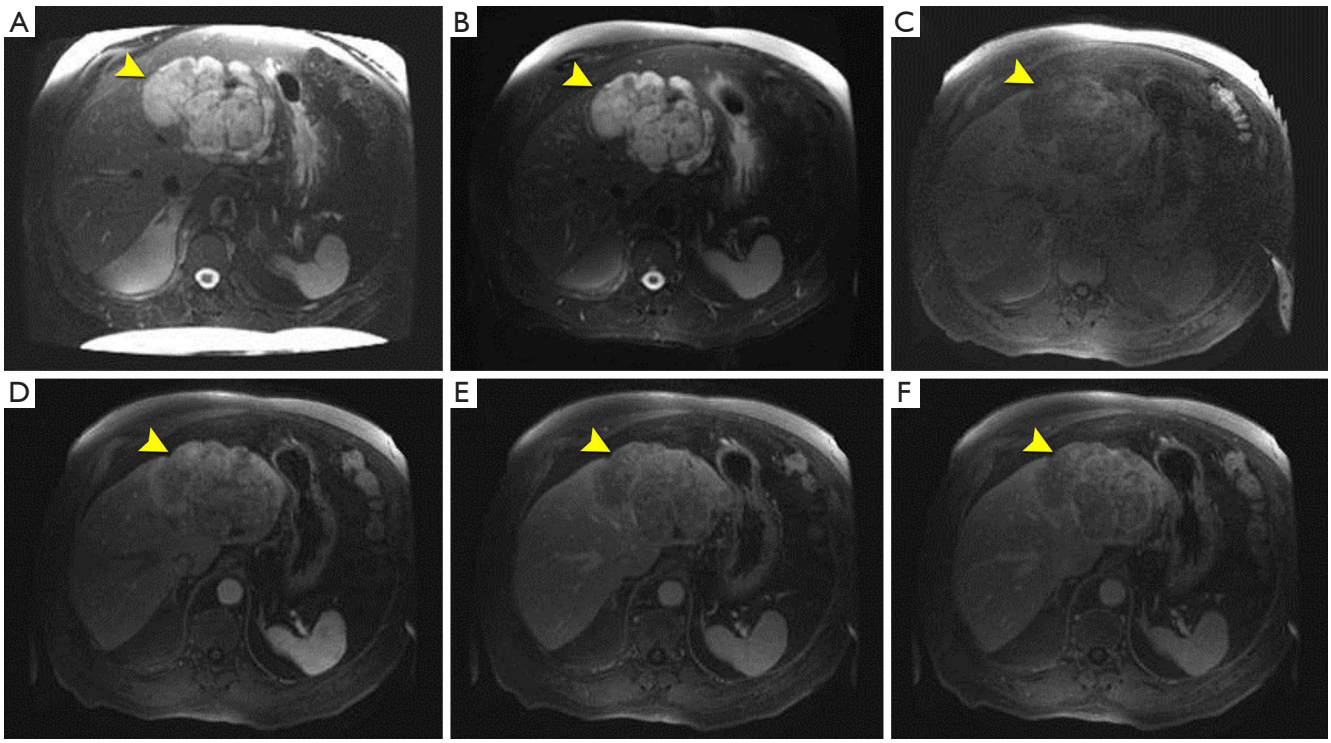

Figure 1 Representative images from the MRI study in Case 1. Axial T2-weighted without fat saturation (A), axial T2-weighted with fat saturation (B), pre-contrast T1-weighted (C) and post-contrast arterial, venous and delayed phase T1-weighted (D-F, respectively) images. Note the mass has a lobulated and septated appearance (yellow arrowheads) with (A,B) heterogeneously increased T2 signal, (C) T1 isointensity to hypointensity, (D) heterogeneous arterial phase enhancement with (E) washout during venous phase and (F) retention of contrast in some regions in delayed phase, likely representing fibrotic regions.

(EGD) with endoscopic ultrasound (EUS) were negative for extrahepatic disease. Review of the outside liver fine needle aspiration (FNA) suggested an epithelial neoplasm with glandular and papillary architecture and mild cytologic atypia suggestive of a low grade adenocarcinoma, possibly of biliary origin, and morphologic features compatible with an adenofibroma. The patient underwent a left hepatectomy, which contained an 11 cm × 10.5 cm × 6 cm soft pink mass encompassing a 9 cm × 3.5 cm × 3 cm firm, white mass. The larger component showed irregularly shaped spaces lined by a single layer of bland, cuboidal epithelium (*Figure 2A*). The firm white area harbored a moderately differentiated adenocarcinoma (*Figure 2B*). A single regional lymph node was negative for tumor. The patient did not develop any recurrence of his malignancy. He passed away nine years later from a new primary lung malignancy.

Case 2

A 71-year-old male was referred to a hepatologist for evaluation of a 5.7-cm caudate lobe mass incidentally discovered on a CT scan. At the time of evaluation, the patient denied weight loss, fever, chills or jaundice. There was no relevant past medical, surgical, family or social history. The patient was overweight with a BMI of 29 kg/m^2 with an unremarkable physical examination. Tumor markers including AFP, CA 19-9 and CEA were not elevated. Liver function tests were within normal limits and he had no serologic evidence of HBV or HCV infection. MRI was performed, which showed a 6.6 cm × 6.3 cm multilobulated, multiseptated cystic mass confined to the caudate lobe (*Figure 3*). There was an enlarged periportal lymph node measuring 3.3 cm concerning for metastasis (not shown). The remainder of the liver had a normal morphologic appearance. The leading diagnosis by imaging was a biliary cystadenocarcinoma and a pre-operative core needle biopsy suggested this diagnosis. The patient underwent surgical resection of the caudate lobe. The multicystic tumor measured 6.3 cm and had subtle transitions to firm gray-red areas laterally (*Figure 4A,B*). The cystic spaces were

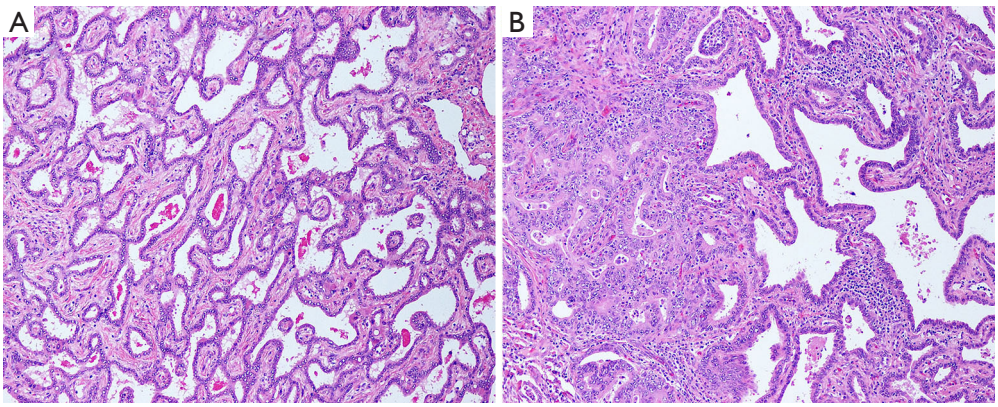

Figure 2 Microscopic pathology of a left hepatic lobe biliary adenofibroma with malignant transformation in Case 1. Photomicrographs of H&E stained sections show (A) cystic spaces lined by bland cuboidal epithelium, in a fibrous stroma (100×, magnification) and (B) transition from benign (right) to malignant neoplasm (left). The invasive component features fused glands lined by cells with pleomorphic nuclei (200×, magnification).

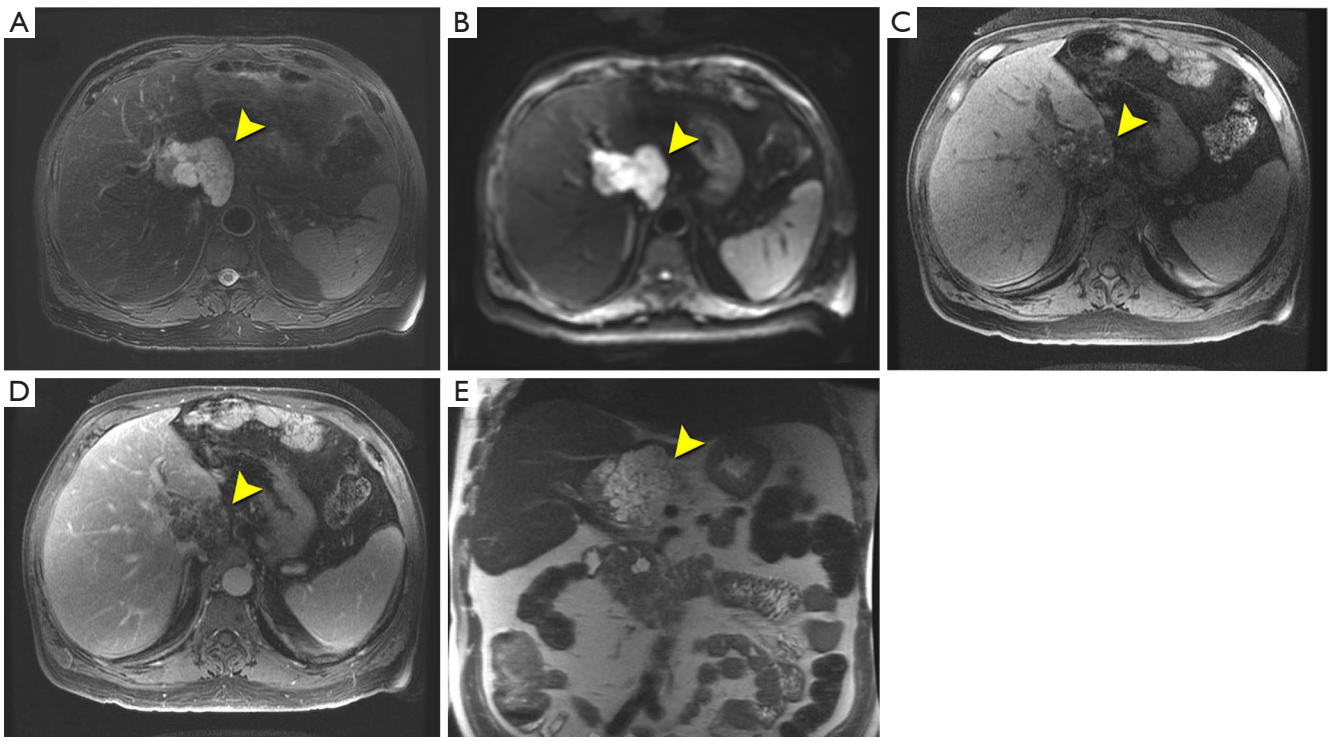

Figure 3 Representative images from the MRI study in Case 2. Axial T2-weighted (A), diffusion weighted (B), pre-contrast T1-weighted (C) and post-contrast portal venous phase T1-weighted (D) images. Note the multilobulated and multiseptated cystic lesion (yellow arrowheads) with (A,E) heterogeneously increased T2 signal, (B) restricted diffusion and (C,D) focal areas of peripheral enhancement on delayed imaging. Additionally, the mass is separate from the pancreas (E).

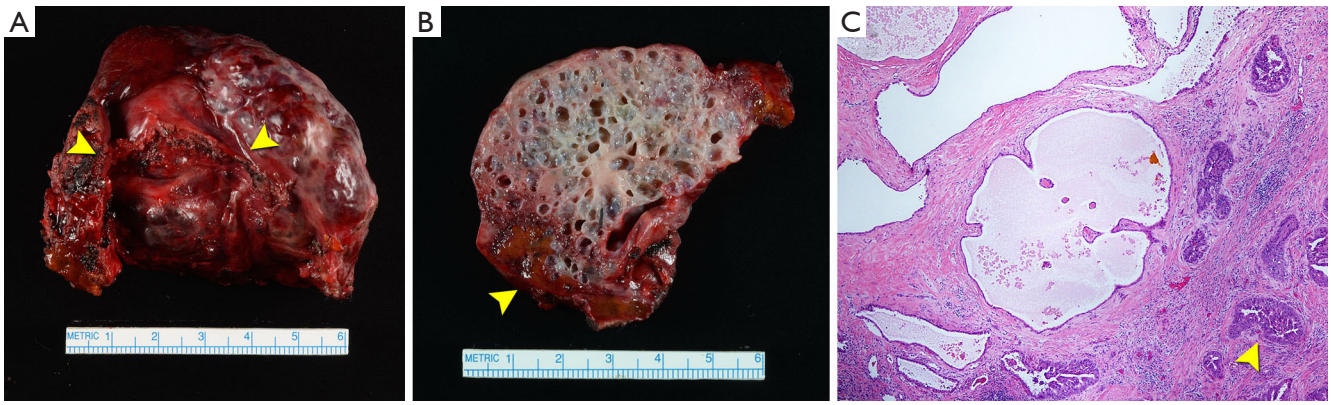

Figure 4 Gross and microscopic pathology of a caudate lobe biliary adenofibroma with malignant transformation in Case 2. (A) Posterior surface of the caudate lobe mass shows the nodular cystic and solid surface of the mass. Note the groove of the inferior vena cava (yellow arrowheads); (B) cross-section of the caudate lobe mass shows a multicystic tumor with intervening white stroma. The darker areas at the left represent transition to adenocarcinoma (yellow arrowhead); (C) photomicrograph of H&E stained section shows cystic spaces in a fibrous stroma, lined by cuboidal epithelium. Invasive adenocarcinoma occupies the lower right corner (yellow arrowhead; 40×, magnification).

lined by low cuboidal epithelium, while the solid areas contained an invasive well-differentiated adenocarcinoma (*Figure 4C*). Eleven regional lymph nodes were negative for tumor. The tumor cells were positive for CK7 and negative for CDX-2 and CK20. The patient has had no evidence of local recurrence by CT at first four-week follow-up. Next generation sequencing of the tumor identified a loss of function (nonsense) mutation (Q50*) in the tumor suppressor protein $p16^{INK4a}$ encoded by the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene.

Discussion

BAF are rare, benign biliary cystic tumors characterized histopathologically by: (I) non-mucin producing, biliary epithelium; (II) tubulocystic architecture; (III) fibrous stroma; and (IV) rare potential for malignant transformation (1). Given their potential for malignant transformation, BAFs are hypothesized to be a precursor to peripheral intrahepatic cholangiocarcinoma (1). Of the eleven prior cases of BAF reported in the literature, six were associated with evidence of malignant transformation (*Table 1*) (1-12).

The imaging findings of a large, liver mass with both cystic and enhancing solid components in a patient without underlying liver disease are consistent with a complex cystic liver lesion and a biliary cystic tumor is to be considered at the top of the differential. The differential diagnosis for biliary cystic tumors includes both benign (e.g., biliary cystadenoma and BAF) and malignant tumors (e.g., biliary cystadenocarcinoma and the malignant transformation of a benign BAF). In our series, the complex cystic appearance and enlarged periportal lymph nodes on imaging were suggestive of a malignant rather than a benign neoplasm, such as a biliary cystadenocarcinoma. However, imaging alone cannot reliably differentiate biliary cystadenoma from cystadenocarcinoma (13). Moreover, the reports that include imaging findings of malignant BAF are similar to other biliary cystic tumors (1-11,13). As such, a tissue diagnosis is needed. Of note, a pre-operative FNA biopsy in the first patient showed an adenocarcinoma, possibly arising in a background of BAF, whereas the biopsy in the second patient was suggestive of a biliary cystadenocarcinoma. However, in both patients, final surgical pathology showed adenocarcinoma arising in a background of BAF, further highlighting the difficulty in making this diagnosis with limited tissue.

Furthermore, it appears to be uncommon for these tumors to metastasize or recur after surgical resection (1,2,10-12). Only one prior report of a malignant BAF developed local recurrence and pulmonary metastasis three years after surgical resection (5,6). Our cases suggest that recurrence or metastasis of benign or malignant BAF is not common, even with large tumors, and that complete surgical resection can be curative (*Table 1*). Nonetheless, longer follow-up is needed. Lastly, the *CDKN2A* mutation identified in the second patient has previously been implicated in the pathogenesis of biliary dysplasia and cholangiocarcinoma and this is the first report of a

Table 1 Clinical, imaging, surgical and pathologic features of 13 biliary adenofibroma reported in the literature

Authors (year)	Age/Sex	Tumor size (cm)	Imaging	Location	Surgery	Evidence of malignant transformation	Follow-up
Tsui *et al.* [1993] (3)	74/F	7	Hypodense, heterogeneous enhancement (CT)	Inferior right hepatic lobe	Wedge resection	No	No recurrence or metastasis at 2-year follow-up
Parada *et al.* [1997] (4)	49/F	7	7.5 cm mass (MRI)	Right hepatic lobe	Partial hepatectomy	No	No recurrence, follow-up time not reported
Haberal *et al.* [2001] (5)	21/M	20	20 cm mass (CT)	Right hepatic lobe	Right hepatectomy	Yes	No recurrence at 2-year follow-up. Developed local recurrence and pulmonary metastasis at 3-year follow-up (reported in Akin and Coskun 2002)
Akin and Coskun [2002] (6)							
Garduño-López *et al.* [2002] (7)	68/M	6	Hypodense (CT)	Left hepatic lobe	Left hepatectomy	No	No recurrence at 50 months follow-up
Varnholt *et al.* [2003] (8)	21/F	16	Enhancing cystic/solid mass (MRI)	Hepatic segments IV, V and VIII	Incomplete central hepatectomy (80% enucleation)	No	No metastasis or significant tumor growth at 3-year follow-up
Gurrera *et al.* [2010] (9)	79/M	5.5	5.5 cm mass (CT)	Right hepatic lobe	Partial liver resection	No	No recurrence or metastasis at 7-year follow-up
Kai *et al.* [2012] (10)	40/M	7	Enhancing cystic/solid mass (CT)	Right hepatic lobe	Right hepatectomy	Likely yes; Strong cytological atypia and invasion; Unclassified multicystic biliary tumor with adenofibroma features	No recurrence of hepatic tumor but patient died of fulminant hepatitis B (HBV) 8 months post-operatively
Nguyen *et al.* [2012] (11)	53/F	6.5	Multicystic/multiseptated mass with septal enhancement (MRI)	Segment IVb	Segmental resection of segments III/IV	Yes	No recurrence or metastasis at 1-year follow-up
Nakanuma *et al.* [2014] (12)	69/F	3.5	None reported	Left hepatic lobe	Not reported	Yes	None reported
Thai *et al.* [2016] (1)	77/M	4	Targetoid mass with peripheral edematous halo and necrotic central area (CT and MRI)	Segment II	Left hepatectomy	Yes	None reported
Godambe *et al.* [2016] (2)	71/F	6.3	Heterogeneous enhancement with multiple areas of low attenuation (CT)	Segments II, III, IVa	Left hepatectomy	Yes	None reported
Thompson *et al.* [2016] (Present Case 1)	71/M	14.5	Cystic/solid mass with areas of peripheral enhancement (MRI)	Left hepatic lobe	Left hepatectomy	Yes	No recurrence or metastasis of liver tumor but patient died 9 years later from a new primary lung malignancy
(Present Case 2)	71/M	6.3	Multilobulated, multicystic and solid mass with areas of peripheral enhancement (MRI)	Caudate lobe	Isolated caudate lobe resection	Yes	No recurrence or metastasis at 1-month follow-up

CDKN2A mutation in a malignant BAF (14). In summary, these two cases highlight that malignant BAF, although rare, should be considered in the differential diagnosis of a complex cystic liver mass consistent with a biliary cystic tumor and may share a similar molecular pathogenesis to other biliary tract malignancies.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: This HIPAA-compliant study was approved by the Institutional Review Board and a waiver of informed consent was granted.

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