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Clinical Case Study

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Adenomyomatosis of the Common Bile Duct and Ampulla of Vater

Catarina Gouveia[a] Catarina Fidalgo[a] Rui Loureiro[a] Helena Oliveira[b] Rui Maio[c] Marília Cravo[a]

[a]Gastroenterology Department, Beatriz Ângelo Hospital, Loures, Portugal; [b]Pathology Department, Beatriz Ângelo Hospital, Loures, Portugal; [c]General Surgery Department, Beatriz Ângelo Hospital, Loures, Portugal

Keywords
Adenomyomatous hyperplasia · Adenomyosis · Adenomyomatosis · Adenomyoma · Ampulla of Vater · Common bile duct

Abstract
Adenomyomatosis is a rare benign lesion that has been observed in different sites throughout the gastrointestinal tract, most frequently in the gallbladder. Few cases have been described in the stomach, small bowel, bile ducts, and ampullary region. Adenomyomas of the vaterian system (ampulla and common bile duct) have important clinical consequences, since the majority of these lesions present with biliary tract obstruction and mimic malignant behavior. As a consequence, considering the diagnostic difficulty of these lesions, patients are often treated with extensive surgery (pancreaticoduodenectomy). We report 2 cases of adenomyomatosis: one of the ampulla of Vater and the other of the common bile duct, as well as a review of reported cases in the literature. Both of our patients presented with epigastralgia and had laboratory or endoscopic evidence of biliary obstruction. Both patients underwent endoscopic ultrasound, one of them with fine-needle aspiration; however, it was not possible to exclude the possibility of cancer. The diagnosis of adenomyoma was only confirmed by the surgical specimen after pancreaticoduodenectomy.

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Adenomiomatose da Via Biliar Principal e Ampola de Vater

Palavras-Chave
Hiperplasia adenomiomatosa · Adenomiose · Adenomiomatose · Adenomioma · Ampola de Vater · Via biliar principal

Resumo
A adenomiomatose é uma lesão benigna rara que tem sido observada em diferentes locais do trato gastrointestinal, mais frequentemente na vesícula biliar. Poucos casos foram descritos no estômago, intestino delgado, vias biliares e ampola de Vater. Os adenomiomas do sistema de Vater (ampola e via biliar principal) têm importantes consequências clínicas, uma vez que a maioria dessas lesões se apresenta com obstrução biliar, sugerindo comportamento maligno. Como consequência, na maioria dos casos, e considerando a dificuldade diagnóstica destas lesões, os doentes são frequentemente submetidos a cirurgia extensa (pancreaticoduodenectomia). Reportamos dois casos de adenomiomatose da ampola de Vater e via biliar principal, bem como uma revisão dos casos descritos na literatura. Os doentes apresentaram-se com queixas de epigastralgia e evidência laboratorial ou endoscópica de obstrução biliar. Em ambos os casos foi re-

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Catarina Gouveia
Gastroenterology Department, Beatriz Ângelo Hospital
Avenida Carlos Teixeira 3
PT–2674-514 Loures (Portugal)
catarinagouveia228@gmail.com

alizada ultrassonografia endoscópica e em um deles punção aspirativa por agulha fina, não tendo sido possível excluir a possibilidade de malignidade. O diagnóstico de adenomioma foi apenas confirmado na peça cirúrgica após pancreaticoduodenectomia.

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Introduction

Adenomyomatosis (adenomyomatous hyperplasia, adenomyosis, or adenomyoma) is a rare benign lesion that has been observed in different sites throughout the gastrointestinal tract, most frequently in the gallbladder [1]. Adenomyomatosis of the gallbladder is most often an incidental finding during cholecystectomy performed for another reason with a prevalence of 1–9%, and large autopsy series report a prevalence of 7% [2, 3]. Few cases have been described in the stomach, small bowel, bile ducts, and ampullary region. Adenomyomas of the vaterian system (ampulla of Vater [AV] and common bile duct [CBD]), unlike its counterparts in the rest of the digestive tract, have important clinical consequences, since the majority of these lesions present with biliary tract obstruction and mimic malignant behavior [1]. As consequence, despite being a benign lesion in most cases, patients are often treated with extensive surgery (pancreaticoduodenectomy). We report 2 cases of adenomyomatosis: one of the AV and the other of the CBD, as well as a review of cases reported in the literature. Both of our patients presented with epigastralgia and had laboratory or endoscopic evidence of biliary obstruction. The diagnosis of adenomyoma was only confirmed by the surgical specimen after cephalic pancreaticoduodenectomy.

Table 1. Full blood workup (case 1)

Parameter	Value
Hemoglobin, g/dL	13.0
White blood cells, $\times 10^9$/L	5,000
Platelets, $\times 10^9$/L	331,000
Urea, mg/dL	18
Creatinine, mg/dL	0.67
AST, IU/L	**72**
ALT, IU/L	**86**
ALK, IU/L	47
GGT, IU/L	26
Total bilirubin, mg/dL	0.26
Conjugated bilirubin, mg/dL	0.17
Amylase, IU/L	70
Serum sodium, mg/dL	140
Serum potassium, mg/dL	4
C-reactive protein, mg/dL	0.1
CA 19.9	6.9

Case Reports

Case 1

A 70-year-old woman with previous laparoscopic cholecystectomy for gallstones and a history of hypertension and dyslipidemia was referred to a gastroenterologist for epigastralgia and an abnormal abdominal CT scan, which revealed CBD dilatation (22 mm) with progressive reduction in size, without any AV or pancreas distortion. She had no family history of cancer and no jaundice. Laboratory workup showed elevated transaminases: 72 IU/L aspartate transaminase (AST) and 86 IU/L alanine transaminase (ALT). Alkaline phosphatase (ALK), γ-glutamyltransferase (GGT), total and conjugated bilirubin, and amylase were within normal ranges. Carcinogen antigen 19.9 (CA 19.9) was normal. She had a normal complete blood count and no elevation in acute-

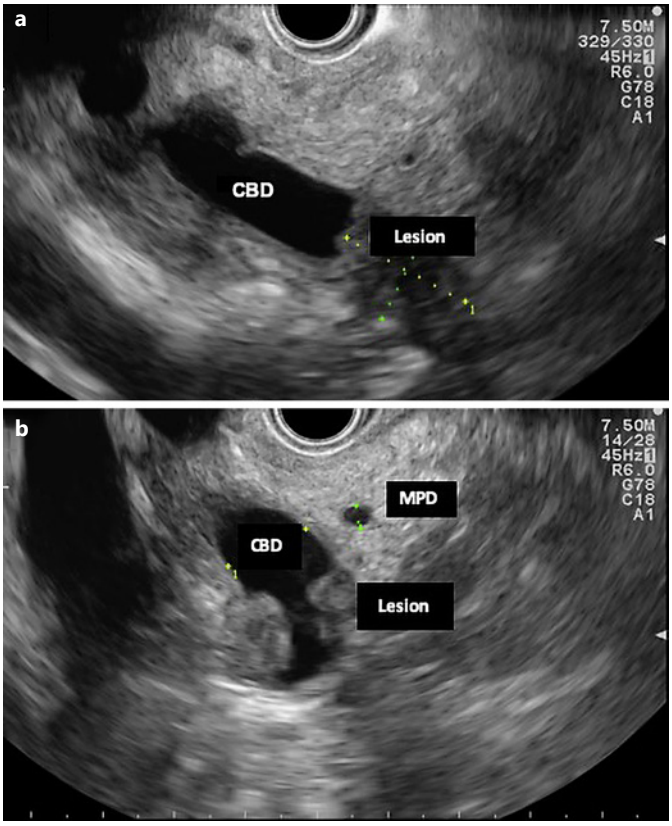

Fig. 1. EUS (linear endoscope) reveals dilated CBD and a poorly defined hypoechogenic mass in its distal portion (**a**). **b** Mass in the distal common bile duct.

phase reactants (Table 1). A magnetic resonance cholangiopancreatography (MRCP) confirmed CBD dilatation with a localized stenosis 1 cm above the ampulla. A subsequently performed endoscopic ultrasound (EUS) showed a dilated CBD (16 mm) and a poorly defined hypoechogenic mass (1.5 × 1.9 cm) in the distal part. There was neither main pancreatic duct (MPD) or parenchyma involvement nor evidence of lymph node, ascites, or left hepatic lobe alterations (Fig. 1). A duodenoscopy showed a bulging AV with normal mucosa (Fig. 2). EUS-guided fine-needle aspiration (FNA) or brush cytology/biopsies obtained by endoscopic retrograde cholangiopancreatography (ERCP) was not performed because a negative or inconclusive histology would not change our therapeutic approach, since malignancy suspicion was high. The case was discussed at a digestive oncology multidisciplinary meeting and in consideration of the diagnostic hypothesis of cholangiocarcinoma of the distal bile duct and after discussion with the patient, she was submitted to a cephalic pancreaticoduodenectomy, which was performed 1 month later. Surgery was uneventful, and the patient was discharged on the 15th postoperative day. Macroscopic examination of the surgical specimen showed a bulging AV, CBP dilatation, and a subepithelial lesion without duodenal wall or pancreas invasion (Fig. 3). Histologically, the lesion consisted of hyperplastic glandular lobules surrounded by muscle fibers and fibroblasts, suggestive of adenomyomatosis of the CBP and AV (Fig. 4). At the 3-year follow-up, she was asymptomatic and without laboratory abnormalities.

Case 2

A 58-year-old man with a history of peptic ulcer disease and gastroesophageal reflux was referred to a gastroenterologist after an upper GI endoscopy, performed for epigastralgia. A protruding ampulla with a normal mucosa was described (Fig. 5). He had no family history of cancer and had no jaundice. Laboratory workup showed elevated transaminases with AST of 52 IU/L and ALT of

Fig. 2. Duodenoscopy showing bulging of the ampulla of Vater with a normal mucosa.

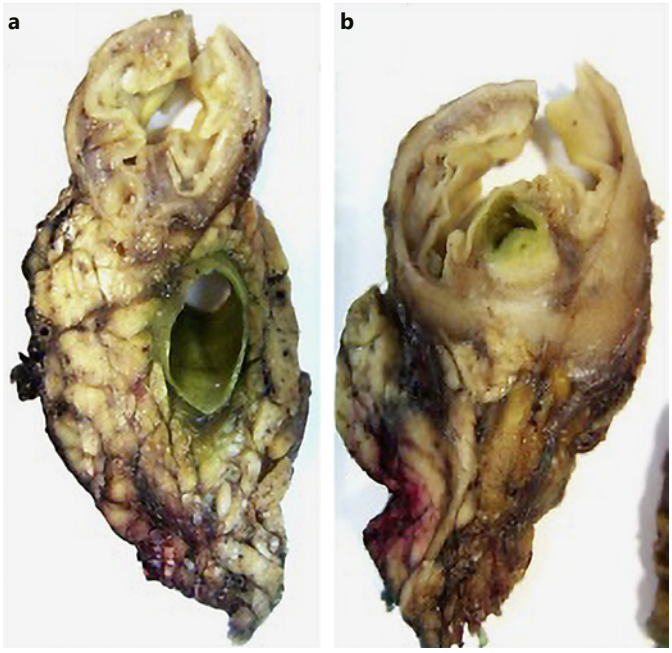

Fig. 3. Macroscopic examination of a surgical specimen shows bulging of the ampulla and CBD dilatation (**a**) and a subepithelial lesion without duodenal wall or pancreas invasion (**b**).

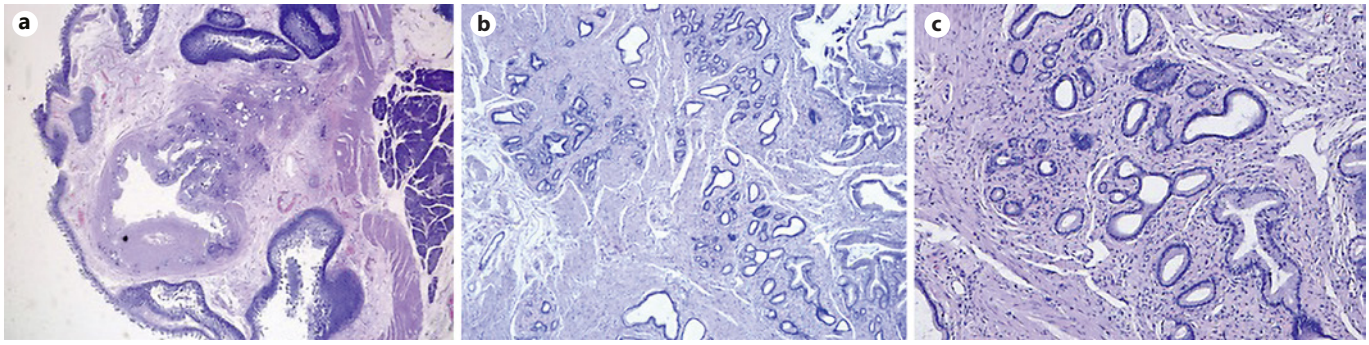

Fig. 4. Microscopic examination of surgical specimens. H&E. **a**. Low magnification with subepithelial lesion. **b** ×4. **c** Hyperplastic glandular lobules surrounded by muscle fibers and fibroblasts. ×10.

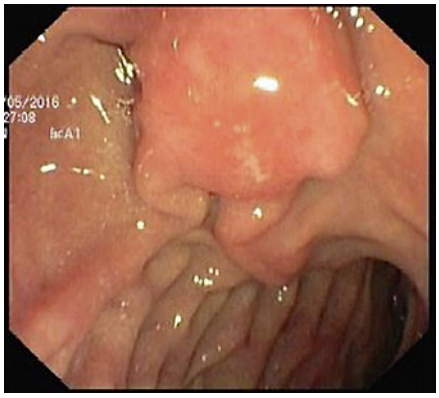

Fig. 5. Duodenoscopy with protruding ampulla with a normal mucosa.

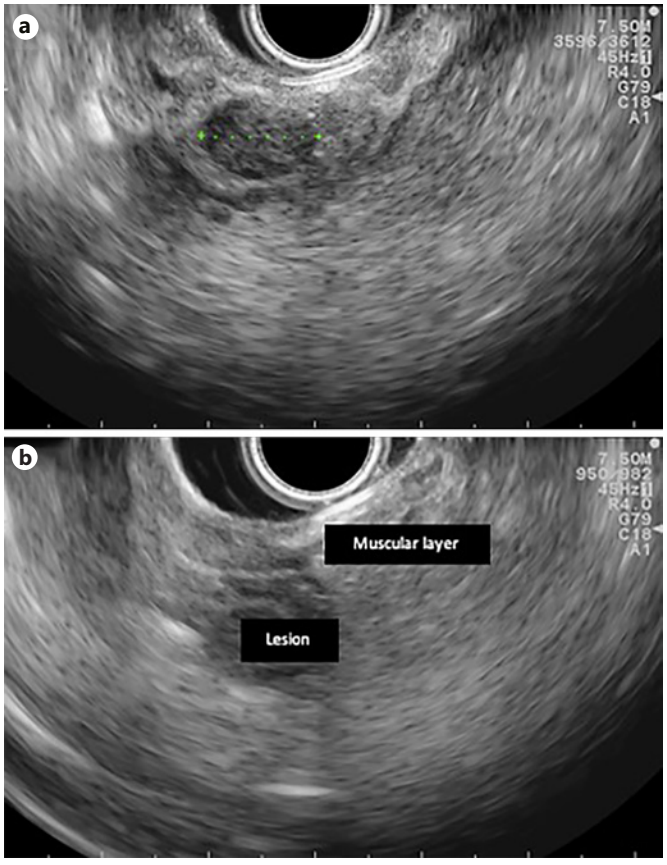

Fig. 6. EUS features (linear endoscope): 12-mm hypoechogenic mass in the ampulla area (**a**) and a lesion with duodenal-wall muscular-layer involvement (**b**).

64 IU/L. ALK, GGT, total and conjugated bilirubin, and amylase were within normal ranges. A complete blood count was normal, and acute-phase reactants were not elevated. CA 19.9 was normal (Table 2). EUS showed a 12-mm, poorly defined, hypoechogenic mass in the AV area, with involvement of the distal CBD and the

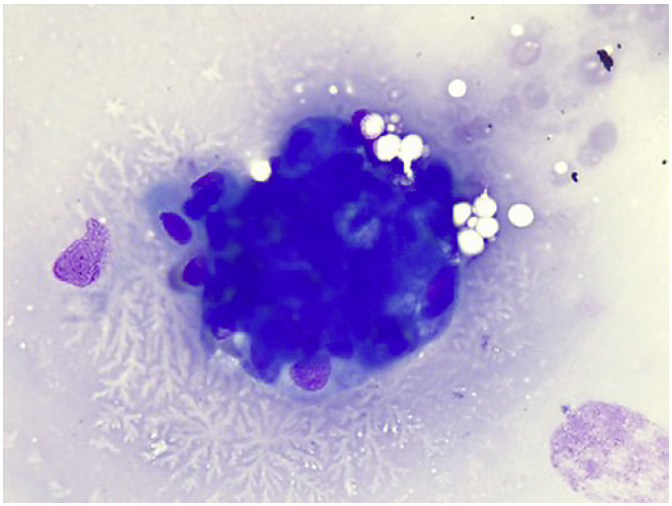

Fig. 7. Cytology examination showed groups of epithelial cells: some with benign characteristics and others with nuclear overlap and increased nuclei in favor of epithelial dysplasia without obvious carcinoma characteristics.

muscular layer of the duodenal wall. There was no evidence of CBD dilatation or pancreatic involvement (Fig. 6). FNA was performed. Cytological examination showed groups of epithelial cells: some with benign characteristics and others with nuclear overlap and increased nuclei, in favor of epithelial dysplasia, without obvious carcinoma characteristics (Fig. 7). The case was discussed at a digestive oncology multidisciplinary meeting; considering the diagnostic hypothesis of ampulloma and after discussing the case with the patient, she was submitted to cephalic pancreaticoduodenectomy, which was performed 1 month later. The surgery was uneventful, and the patient was discharged on the 8th postoperative day. Macroscopic examination of the surgical specimen showed a white and firm tumor of 1.6 cm in largest diameter (Fig. 8). Histologically (Fig. 9), there was a slight CBD and MPD dilatation and some inflammatory infiltrate. The ampulla consisted of aggregates of ductal proliferation surrounded by fibrosis, which had continuity with the muscular layer of the duodenal wall. There were some areas with enlarged and stratified nuclei in favor of reactive atypia. These findings were consistent with the diagnosis of AV adenomyomatosis. At the 2-year follow-up, she was asymptomatic and without analytical alterations.

Discussion

According to the WHO classification, adenomyoma is a benign lesion with no premalignant risk, defined as duct-like structures accompanied by hyperplasia of smooth muscle bundles [4]. The real incidence of these lesions is difficult to settle as different names are used to designate the same histological lesion [1]. Published series of unselected postmortem examinations report an in-

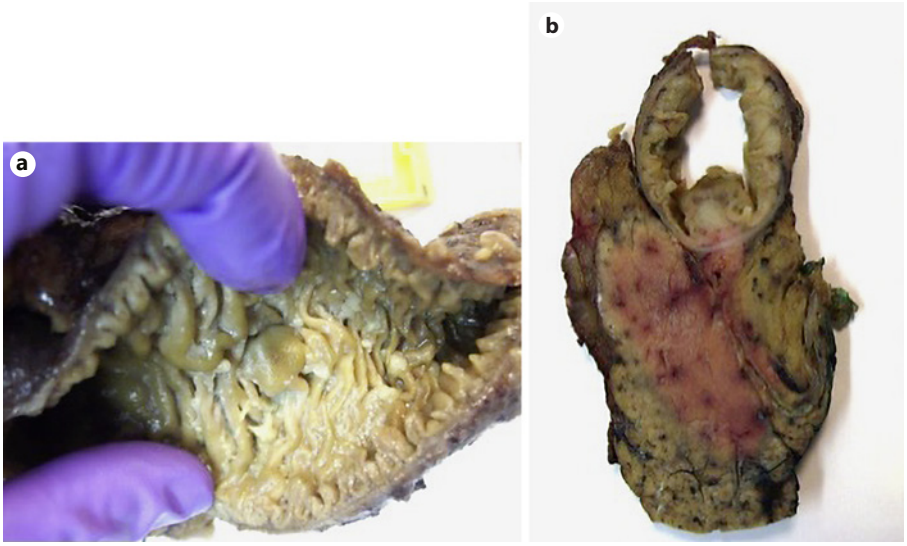

Fig. 8. Macroscopic examination of a surgical specimen: bulging ampulla (**a**) and white and firm tumor 1.6 cm in the largest diameter (**b**).

cidence of 50–70% of small adenomyomas of the vaterian system (<5 mm), a high percentage of cases having no relevant associated clinical history. Symptomatic lesions reported in the medical literature are much rarer and reported mostly as single case reports [5, 6]. To our knowledge, this is the first literature review regarding AV and CBD adenomyomatosis. Our 2 cases were a 70-year-old woman and 58-year-old man with laboratory or endoscopic evidence of biliary obstruction, in whom preoperative diagnosis was ambiguous, and the diagnosis of adenomyoma was only confirmed by the surgical specimen after pancreaticoduodenectomy.

A PubMed search conducted using the key words "adenomyomatous hyperplasia," "adenomyoma," "adenomyosis," "adenomyomatosis," and "ampulla of Vater" or "common bile duct," revealed 61 case reports (from 1987 to July 2018) eligible for analysis (Table 3). Regarding published cases, almost half of the patients were male (n = 29, 48%), and their mean age was 62 years (range 18–81 years). Forty-nine patients had AV adenomyoma (80%), and 12 had CBD adenomyoma (20%). Patients presented with jaundice (n = 22/61), abdominal pain (n = 25/61), nausea and vomiting (n = 3/61), acute pancreatitis (n = 2/61) – both with AV lesions, loss of appetite (n = 3/61), and fatigue (n = 1). Fifteen patients (25%) were asymptomatic, and the finding was incidental. For 1 patient, clinical presentation was not mentioned. Nineteen patients had cholestasis/conjugated hyperbilirubinemia, 10 had transaminase, ALK, or GGT elevation with normal bilirubin, 2 patients had elevated amylase and lipase, and 3 patients had normal liver tests. In 26 cases, laboratory workup was not reported. Imaging (abdominal CT, MRI, and MRCP) and endoscopic (ERCP and upper GI EUS) features more frequently found were CBD or MPD dilation, tumor-like mass in the papilla region or distal CBD, CBD stenosis, intrahepatic biliary tract dilation, and bulging papilla (in patients with ampullary lesions). There was no preoperative or intraoperative histological diagnosis in 26 patients. In the other patients, several different diagnoses were made: 2 adenomas, 5 adenocarcinomas, 2 cases of inflammatory changes, 3 cases of dysplasia, 3 cases of atypical cells, 3 cases of muscular and glandular proliferation, 1 case of suspected adenomyoma, 8 adenomyomas, 1 adenomyoma with dysplasia, and 1

Table 2. Full blood workup (case 2)

Parameter	Value
Hemoglobin, g/dL	15.2
White blood cells, $\times 10^9$/L	6,000
Platelets, $\times 10^9$/L	219,000
Urea, mg/dL	18
Creatinine, mg/dL	0.83
AST, IU/L	**52**
ALT, IU/L	**64**
ALK, IU/L	40
GGT, IU/L	21
Total bilirubin, mg/dL	0.44
Conjugated bilirubin, mg/dL	0.12
Amylase, IU/L	90
Serum sodium, mg/dL	136
Serum potassium, mg/dL	3.9
C-reactive protein, mg/dL	0.2
CA 19.9	1.3

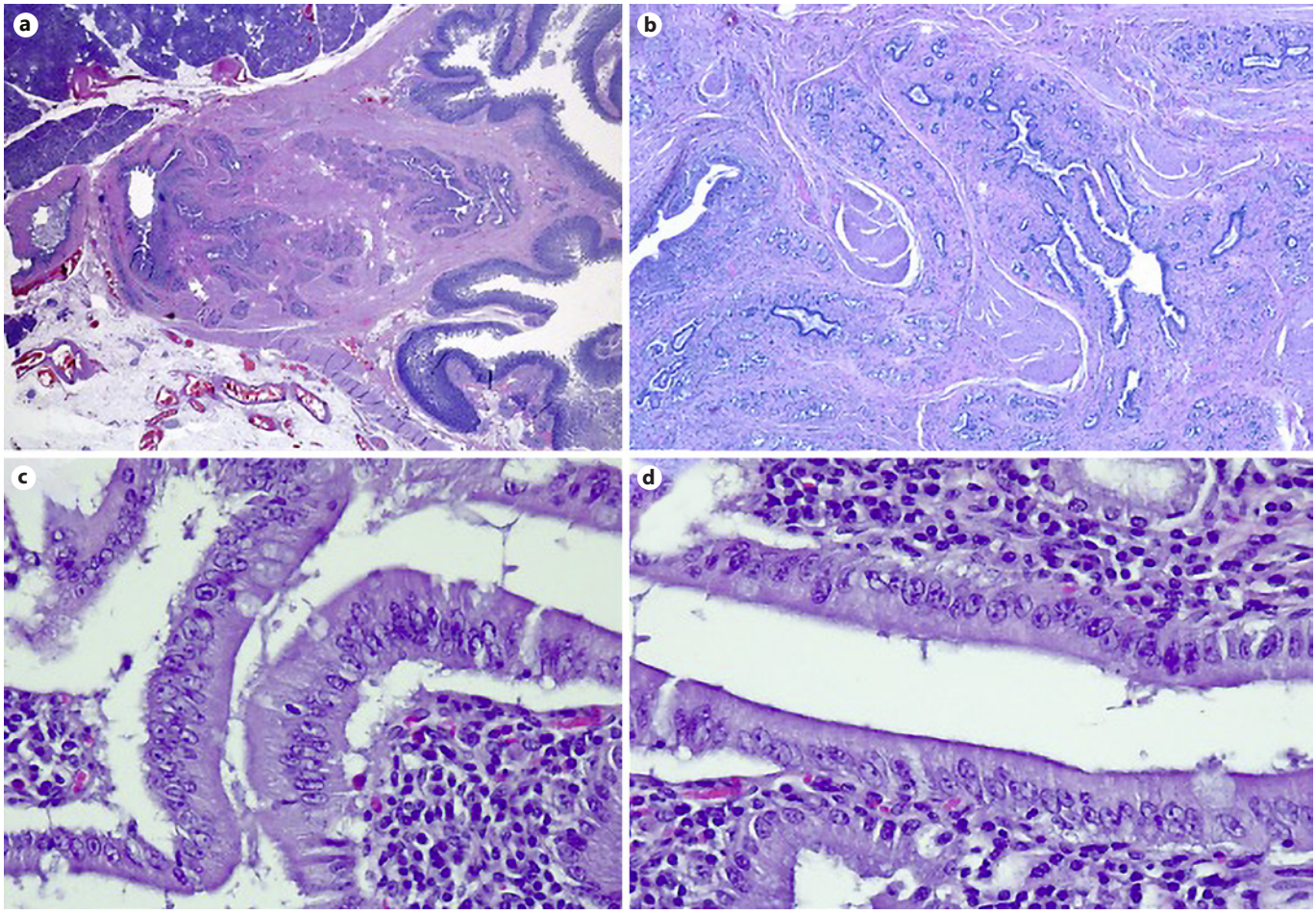

Fig. 9. Microscopic examination of the specimen. H&E. **a** Low magnification showing that the lesion consisted of aggregates of ductal proliferation surrounded by fibrosis and had continuity with the muscular layer of the duodenal wall. **b** Low magnification demonstrates slight dilatation of CBD and MPD, and chronic periductal inflammatory infiltrate. **c**, **d** Areas with enlarged and stratified nuclei in favor of reactive changes. ×40.

patient without malignant cells. Besides these pre-/intraoperative diagnoses, in 6 patients, intraoperative frozen sections revealed adenomyomatosis of ampullary, glandular, and muscular proliferation, muscle-cell hyperplasia, uncertain for malignancy, atypical cells, and negative for malignancy, respectively. Consequently, only in 9 patients (15%), adenomyoma was diagnosed pre-/intraoperatively. These patients were submitted to endoscopic papillectomy (n = 4), surgical papillectomy (n = 1), and close observation (n = 4). Forty-one patients (67%) underwent duodenopancreatectomy, 7 patients were submitted to endoscopic ampullectomy, 2 patients underwent surgical ampullectomy, 2 had local surgical/extensive excision, 2 had CBD surgical resection, 1 had endoscopic mass excision using biopsy forceps, and 4 patients received close observation with repeated endoscopic observations (lesions did not change with time, but the duration of follow-up time is mentioned in the case report).

The diagnosis of adenomyoma of the vaterian system (AV and CBD) is challenging. Patients often present with signs of biliary obstruction and cholestasis, and preoperative imaging (CT, MRI, and MRCP) frequently shows common bile duct obstruction or a tumor-like mass. Endoscopic biopsies, EUS-FNA and brush cytology show most of the time atypical cells, dysplasia, or even malignancy. In retrospect, these findings are thought to be secondary to AV and CBD endoscopic manipulation (biopsy, brush cytology, and sphincterotomy), and may contribute to the diagnostic difficulties. The overall accuracy for preoperative histopathological diagnosis with endoscopic forceps biopsies in patients with AV tumors was reported

Table 3. Literature review of adenomyomatosis of the ampulla of Vater (AV) and common bile duct (CBD)

Reference	Age, sex	Location	Clinical presentation	Laboratory changes	Imaging/endoscopic features	Pre-/intraoperative histologic diagnosis	Treatment/ management
Uljch et al. [20], 1987	Elderly, F	AV	NA	Biliary obstruction	Recent onset of CBD dilatation	Not made	Extensive surgical resection
Ikei et al. [21], 1989	71, F	CBD	Jaundice, fever and abdominal pain	Conjugated hyperbilirubinemia (6.8 mg/dL), ↑ ALK (123 IU/L), ↑ AST (54 IU/L), ↑ ALT (95 IU/L)	CT: dilation of intra- and extrahepatic duct; PTC: dilation of CBD and stenosis of its distal part	Not made	PD
Ikei et al. [21], 1989	52, F	CBD	Abdominal pain	Normal	ERCP: dilated CBD (17 mm) with mural irregularity (about 26 mm long) and a spherical immobile shadow defect at the end of the bile duct	Not made	PD
Legakis et al. [22], 1990	55, F	CBD	Jaundice and abdominal pain	Conjugated hyperbilirubinemia (5.7 mg/dL), ↑ ALP (1,700 IU/L)	Not made	Not made	Choledochal excision and hepaticojejunal anastomosis
Läuffer et al. [23], 1998	69, F	CBD	Abdominal pain	Normal	ERCP: hemispherical contrast defect in the terminal CBD 1.5 cm proximal to the papilla of Vater	Biopsies: suggestive of adenoma, but not conclusive; brush cytology: no malignant cells; frozen sections indicated benign hyperplasia of muscle cells without evidence of malignancy	Surgical local tumor excision in the distal CBD through the papilla of Vater
Narita et al. [19], 1999	73, F	AV	Jaundice	NA	US: dilated CBD (15 mm); CT scan showed a tumor-like mass in the papilla of Vater	Not made	CPD
Kalil et al. [24], 2000	18, M	AV	Jaundice and abdominal pain	Conjugated hyperbilirubinemia (26 mg/dL), ↑ AST (87 IU/L), ↑ ALT (53 IU/L), ↑ GGT (247 IU/L)	CT: dilation of CBD (17 mm), IOC: CBD dilation and a periampular mass (20 mm)	Not made	CPD
Tsukamoto et al. [25], 1999	31, F	CBD	Epigastralgia	Cholestasis	Stenosis of the CBD	Not made	Resection of the CBD with choledochojejunostomy
Ojima et al. [26], 2000	64, F	CBD	Jaundice, abdominal pain, fever and appetite loss	NA	ERCP: possible stenosis in the distal CBD	Not made	DP
Kayahara et al. [27], 2001	42, F	AV	Abdominal pain	↑ AST (63 IU/L), ↑ ALT (113 IU/L), ↑ GGT (173 IU/L)	ERCP: abnormal shadow in the periampullary region; PTC: choledochal obstruction; IOC: lack of contrast passage to duodenum and CBD dilation	Papilla biopsy: mucosal hyperplasia; intraoperative frozen section: adenomyomatosis of the ampulla	Surgical papillotomy and sphincteroplasty
Bedirli et al. [28], 2002	63, M	AV	Epigastric pain	Conjugated hyperbilirubinemia (4.2 mg/dL), ↑ ALP (397 IU/L)	CT: dilated CBD and an AV mass (2.5 × 2.0 cm); ERCP: CBD and MPD dilation	Intraoperative frozen section ruled out malignancy	DP

Table 3 (continued)

Reference	Age, sex	Location	Clinical presentation	Laboratory changes	Imaging/endoscopic features	Pre-/intraoperative histologic diagnosis	Treatment/ management
Bedirli et al. [28], 2002	51, M	AV	Jaundice	Conjugated hyperbilirubinemia (11.7 mg/dL), ↑ ALP (958 IU/L)), ↑ AST (60 IU/L), ↑ ALT (92 IU/L)	CT: intrahepatic biliary dilation and dilated CBD (17 mm), possible mass in the head of the pancreas	Not made	DP
Handra-Luca et al. [1], 2003	64, M	AV	Abdominal pain	NA	Heterogenous intra-ampullary lesion (11 mm)	Brush cytology: atypical cells	DP
Handra-Luca et al. [1], 2003	61, M	AV	Jaundice and epigastric pain	NA	No lesion	Adenoma	DP
Handra-Luca et al. [1], 2003	73, M	AV	Asymptomatic	NA	Intra-ampullary lesion (21 mm)	Inflammatory changes	DP
Handra-Luca et al. [1], 2003	67, F	AV	Jaundice	NA	Intra-ampullary lesion (15 mm)	Adenocarcinoma	DP
Handra-Luca et al. [1], 2003	54, F	AV	Asymptomatic	NA	Intra-ampullary lesion (20 mm)	Adenoma	DP
Handra-Luca et al. [1], 2003	55, M	AV	Asymptomatic	Cholestasis	Hypoechogenic intra-ampullary lesion (15 mm)	Severe dysplasia	DP
Handra-Luca et al. [1], 2003	71, F	AV	Right upper quadrant pain	NA	Hyperechogenic intra-ampullary lesion (10 mm)	Muscle fibers, glandular structures	DP
Handra-Luca et al. [1], 2003	78, F	AV	Jaundice	Cholestasis	Tumor located in the pancreas head	Not made	DP
Handra-Luca et al. [1], 2003	49, F	AV	Right upper quadrant pain	NA	NA	Hyperplastic glandular structures, inflammatory changes	DP
Handra-Luca et al. [1], 2003	38, F	AV	Abdominal pain	NA	NA	Low-grade dysplasia	DP
Handra-Luca et al. [1], 2003	67, M	AV	Jaundice	NA	Thickening of the terminal CBD wall	Not made	DP

Table 3 (continued)

Reference	Age, sex	Location	Clinical presentation	Laboratory changes	Imaging/endoscopic features	Pre-/intraoperative histologic diagnosis	Treatment/ management
Handra-Luca et al. [1], 2003	74, M	AV	Jaundice	NA	Heterogenous intra-ampullary lesion (20 mm)	Not made	DP
Handra-Luca et al. [1], 2003	72, F	AV	Asymptomatic	NA	Intra-ampullary lesion (10 mm)	Adenocarcinoma	DP
Aoun et al. [16], 2005	68, M	AV	Jaundice and epigastric pain	NA	CT: hypoattenuating lesion in the ampullary region slightly indenting the duodenal lumen (17 × 20 mm)	Not made	CPD
Aoun et al. [16], 2005	71, M	AV	Right upper-quadrant pain	NA	CT: hypoattenuating lesion in the ampullary region (10 × 10 mm) and a dilated pancreatic duct; ERC: distal CBD stenosis	Not made	CPD
Aoun et al. [16], 2005	66, F	AV	Epigastric pain	NA	CT: 14 × 10 mm lesion protruding into the duodenal lumen	Not made	CPD
Martinez Vieira et al. [29], 2005	22, M	AV	Jaundice and weight loss	Conjugated hyperbilirubinemia (4.5 mg/dL), ↑ AST (122 IU/L)	CT: dilated CBP (10 mm) with a stop sign 2 cm above the ampulla; EUS: bulging ampulla, stenosis of distal CBP	Brush cytology: negative for malignancy; intraoperative biopsies: cell of uncertain malignancy	CPD
Massom et al. [30], 2006	73, F	AV	Nausea, vomiting and diarrhea	NA	CT: oval cystic lesion (1.8 × 1.2 cm) in the uncinate process of the pancreas, surrounded by normal-appearing pancreatic tissue	EUS with targeted biopsy: 2 cell populations, one composed of benign-appearing duct-epithelial cells and the other consisting of an occasional focus of atypical cells with loss of polarity and necrosis	CPD
Kwon et al. [31], 2007	74, F	AV	Acute recurrent pancreatitis	↑ AST (47 IU/L), ↑ ALT (49 IU/L), ↑ amylase (4,290 IU/L), lipase (1,526 IU/L)	MRCP: dilated CBD, with distal stenosis; ERCP: bulging papilla, after sphincterotomy, a nodular mass with a granular and villous mucosa originating from the peripancreatic orifice	Muscle proliferation without atypia	Piecemeal endoscopic resection of the mass with electrocautery snare and coagulation of the remnant villous mucosa with argon plasma
Shu et al. [32], 2008	51, M	CBD	Jaundice, nausea, and weight loss	↑ ALT (250 IU/L), ↑ AST (102 IU/L), ↑ ALK (641 IU/L), ↑ GGT (854 IU/L), total bilirubin (1.9 mg/dL)	MRCP: dilatation of the CBD and pancreas duct, irregular stricture of the bile duct and a 1.6 × 0.27 cm mass at pancreatic segment of CBD	Not made	DP
Iwaki et al. [33], 2008	62, F	CBD	Asymptomatic	↑ ALK	CT: thickening of the lower CBD wall; ERCP: a 15-mm-long stenosis of the lower CBD	Bile/brush cytology: no malignant cells	DP
Genevay et al. [34], 2009	73, M	AV	Jaundice	↑ ALK (997 IU/L), ↑ bilirubin (17 mg/dL)	CT: dilated intrahepatic bile ducts; ERCP: 40-mm-long CBD stricture	Not made	DP
Lehwald et al. [35], 2010	42, M	AV	Nausea and vomiting	CA 19.9 normal	CT: a mass in the pancreas head and duodenum with duodenal and distal bile duct stenosis	Intraoperative frozen section: atypical cells	DP

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Table 3 (continued)

Reference	Age, sex	Location	Clinical presentation	Laboratory changes	Imaging/endoscopic features	Pre-/intraoperative histologic diagnosis	Treatment/ management
Higashi et al. [36], 2010	67, F	AV	Jaundice	NA	NA	Suspected adenomyoma	DP
Higashi et al. [36], 2010	78, F	AV	Asymptomatic	NA	NA	Not made	DP
Higashi et al. [36], 2010	49, M	AV	Asymptomatic	NA	NA	Vater carcinoma	DP
Higashi et al. [36], 2010	58, F	AV	Jaundice	NA	NA	Vater carcinoma	DP
Higashi et al. [36], 2010	68, M	AV	Jaundice	NA	NA	Vater carcinoma	DP
Kumari et al. [37], 2011	58, M	AV	Abdominal pain	NA	CBD dilatation	Not made	DP
Kumari et al. [37], 2011	65, M	AV	Jaundice	NA	CBD dilatation	Not made	DP
Kumari et al. [37], 2011	81, M	AV	Appetite loss	NA	CBD dilatation and nodule at ampulla (1.5 × 1 cm)	Not made	DP
Choi et al. [38], 2013	70, M	AV	Abdominal pain	↑ ALT (78 IU/L) ↑ ALK (268 IU/L)	CT: ampullary lesion and CBD dilation (14 mm); endoscopy: ampullary mass with granularity (15 mm)	Endoscopic biopsy: adenomyoma	Endoscopic papillectomy
Choi et al. [38], 2013	71, M	AV	Abdominal pain	↑ ALT (55 IU/L) ↑ AST (92 IU/L) ↑ ALK (432 IU/L) ↑ total bilirubin (1.83 mg/dL)	Endoscopy: ampullary mass (12 mm)	Endoscopic biopsy: adenomyoma	Endoscopic papillectomy
Choi et al. [38], 2013	72, M	AV	Asymptomatic	↑ ALK 180	CT: well-defined nodule at ampulla (15 × 12 mm) and CBD dilatation (13 mm)	Endoscopic biopsy: dysplasia, adenomyoma	Endoscopic papillectomy
Choi et al. [38], 2013	53, M	AV	Abdominal pain	↑ ALK (300 IU/L) ↑ total bilirubin (1.46 mg/dL)	Endoscopy: lobulated lesion of the ampulla (10 mm)	Endoscopic biopsy: chronic inflammation, adenomyoma	Endoscopic papillectomy
Choi et al. [38], 2013	75, M	AV	Asymptomatic	↑ ALK (230 IU/L)	CT: focal enhancing lesion at ampulla with CBD dilatation (11 mm); endoscopy: bulging and lobulated papilla	Endoscopic biopsy: adenomyoma	Surgical ampullectomy
Choi et al. [38], 2013	75, F	AV	Asymptomatic	↑ ALK (251 IU/L)	11-mm mass of the ampulla and CBD dilatation (10 mm); endoscopy: bulging and lobulated papilla	Endoscopic biopsy: adenomyoma	Close observation
Choi et al. [38], 2013	64, F	AV	Asymptomatic	↑ ALK (178 IU/L)	Endoscopy: CBD dilatation (10 mm) and bulging papilla	Endoscopic biopsy: adenomyoma	Close observation
Choi et al. [38], 2013	57, F	AV	Asymptomatic	↑ ALK (174 IU/L) ↑ total bilirubin (1.02 mg/dL)	Endoscopy: enlarged and lobulated papilla	Endoscopic biopsy: atypical epithelial proliferation – adenomyoma	Close observation
Choi et al. [38], 2013	65, F	AV	Asymptomatic	↑ ALK (273 IU/L)	Endoscopy: bulging and lobulated papilla	Endoscopic biopsy: adenomyoma	Close observation

Table 3 (continued)

Reference	Age, sex	Location	Clinical presentation	Laboratory changes	Imaging/endoscopic features	Pre-/intraoperative histologic diagnosis	Treatment/ management
Rafiullah et al. [39], 2014	61, M	AV	Acute pancreatitis	↑ AST (190 IU/L), ↑ ALT (169 IU/L), ↑ ALK (147 IU/L), ↑ amylase (1,855 IU/L), ↑ lipase (285 IU/L)	CT: acute pancreatitis with a peripancreatic adenopathy, dilatation of CBD (10 mm) with abrupt discontinuation at the pancreas head and mildly dilated pancreatic duct (4 mm) at the pancreas head; EUS: multilobulated hypoechoic ampullary density (2.4 × 2.1 cm)	EUS-FNA: reactive cells; endoscopic biopsies: inflammatory polyp versus inflammatory changes overlying an unsampled neoplastic lesion	Endoscopic ampulectomy
Choi et al. [40], 2016	42, M	CBD	Jaundice, epigastric pain and vomiting	Conjugated hyperbilirubinemia (7.8 mg/dL), ↑ ALK (689 IU/L), ↑ GGT (1,199 IU/L), ↑ AST (224 IU/L), ↑ALT (266 IU/L)	CT: abrupt narrowing of the distal CBD and proximal bile duct dilatation	Endobiliary biopsies: chronic inflammation with fibrosis, periductal glandular proliferation, dysplastic change; slightly positive for p53	DP
D'Assuncao et al. [41], 2016	50, F	CBD	Abdominal pain	Liver tests were normal	MRI: dilated CBD; EUS: hypoechoic lesion near the papilla (5.2 mm)	Not made	Endoscopic excision using biopsy forceps
Keegan et al. [42], 2017	59, M	AV	Fatigue	↑ AST (160 IU/L), ↑ ALT (61 IU/L), ↑ GGT (63 IU/L)	CT: hypodensity (10 mm) at the AV with prominent extrahepatic biliary duct; duodenoscopy: a bulky ampulla; EUS: dilated extrahepatic biliary duct (11 mm) with hypoechoic ampullary lesion (13.5 mm)	Not made	Endoscopic ampullectomy
Gialamas et al. [43], 2018	73, F	AV	Jaundice and fatigue	↑ AST (1,008 IU/L), ↑ ALT (1,105 IU/L), ↑ ALK (153 IU/L), ↑ GGT (114 IU/L), conjugated hyperbilirubinemia (21.6 mg/dL)	MRCP: stenosis of the distal CBD at AV level, with dilatation (10 mm) above this region; EUS: retro-ampullary mass	Ampullary mass biopsies: atypical cells and chronic inflammation of the ampulla, without dysplasia	CPD
Gouveia et al., 2019	58, M	AV	Epigastralgia	↑ AST (52 IU/L), ↑ ALT (64 IU/L)	Endoscopy: bulging papilla; EUS: mass (12 mm) in the ampulla area, with distal CBD and apparently duodenal wall muscular involvement	EUS-FNA: epithelial cell groups, some with benign characteristics, others with nuclear overlap and increased nuclei in favor of epithelial dysplasia, without obvious carcinoma characteristics	CPD
Gouveia et al., 2019	70, F	CBD	Epigastralgia	↑ AST (72 IU/L), ↑ ALT (86 IU/L)	CT: CBD dilatation (22 mm) with progressive reduction in size; MRCP: CBD dilatation with a localized stenosis 1 cm above the ampulla; EUS: dilated CBD (16 mm) and a poorly defined hypoechogenic mass (1.5 × 1.9 cm) in the distal CBD	Not made	CPD

CPD, cephalic pancreaticoduodenectomy; DP, duodenopancreatectomy; IOC, intraoperative cholangiography; PTC, percutaneous transhepatic cholangiography.

as 62% by Menzel et al. [7]. Hammarström et al. [8], in a study including 3,131 patients submitted to ERCP, showed that a correct endoscopic diagnosis was only made in 2 of the 4 patients with adenomyoma. ERCP also allows for brush cytology and intraductal biopsy performance. The sensitivity of brush cytology and intraductal biopsy in diagnosing malignant biliary strictures are reported as 45 and 48.1% respectively, and both techniques are almost 100% specific. A combination of both modalities modestly increased the sensitivity to 59.4% [9]. To overcome this limitations, Kim et al. [10] and Uchida et al. [11] showed that repeated testing (multiple cytology tests) via endoscopic nasobiliary drainage increased the cumulative diagnostic rate, with a sensitivity of 95% with 6 repeated exams [10, 11]. Logrono et al. [12], who analyzed 183 pancreatobiliary brush specimens from 2 university hospitals, showed that the possibility of malignancy with no evidence of malignancy from repetitive endoscopic biopsy was lower than 10%. EUS-FNA can be performed for distal extrahepatic bile duct strictures, with a sensitivity and negative likelihood ratio for diagnosis of malignancy of 66% and 0.34, respectively [13]. Furthermore, EUS-FNA can be performed in ampullary and distal CBD masses with an overall accuracy of 100%, with a sensitivity, specificity, and positive and negative predictive values of 100% [14]. Intraoperative frozen sections from the mass can usually differentiate whether the lesion is benign or malignant (adenomyoma and adenocarcinoma). However, most pathologists have limited experience with frozen-section adenomyomas [15]. Macroscopically, adenomyoma of the ampullary region usually appears as a rounded, well-defined, intraluminal lesion arising from the CBD wall, although some case reports have described a diffuse form infiltrating the CBD wall which resembles a stenotic lesion [16]. The histological aspect of adenomyoma is characterized by multiple lobules of glands, mainly located in the muscle layers of the vaterian system. The lobular formations consist of small glands arranged around a larger gland and surrounded by myofibroblastic and fibroblastic proliferation. This mesenchymal component is rather composed of fibroblasts and myofibroblasts (with smooth muscle actin expression but without desmin expression), but it may contain sparse smooth muscle cells [1]. The histogenesis of adenomyoma and adenomyomatous hyperplasia is still a subject of controversy. The most widely accepted hypothesis is that these lesions may represent a form of incomplete heterotopic pancreas (type III), as described by von Heinrich in 1909 [1]. The presence of hyperplastic smooth muscle tissue can be explained by secondary muscle proliferation caused by some stimulus emanating from misplaced epithelium, by muscle misarrangement, or by aberrant growth invading and distorting normal muscle [1]. Martin et al. [17] compared adenomyoma of the vaterian system to its gallbladder counterpart and claimed that the former is a lesion developed in diverticula, accompanied by reactive muscle hyperplasia and secondary gland formation, which leads to poorly defined lobules. Fernandez-Cruz and Pera [18] considered adenomyoma as part of an involutive process of fibroadenomatous type due to increasing age. Other authors, such as Narita and Yokoyama [19], stress the possibly inflammatory nature of this lesion.

Conclusion

Adenomyomatosis of CBD and AV are rare benign lesions, which pose a diagnostic challenge, as they often present with biliary obstruction and mimic malignant neoplasms; imaging and endoscopy rarely offer a definitive diagnosis. As a consequence, in most cases, patients are treated with extensive surgery despite its benign nature. The development and application of new endoscopic, radiological, and pathological modalities are necessary in order to improve the diagnosis and management of these lesions.

Statement of Ethics

The patients have given written informed consent to publish the details of their case (including the publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Catarina Gouveia: acquisition and interpretation of clinical data for and drafting of the case report; *Catarina Fidalgo* and *Marília Cravo:* conception and design of the case; critically revision of the report; and final approval of the version to be published. *Rui Loureiro, Helena Oliveira,* and *Rui Maio:* critical revision of the report and final approval of the version to be published.

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