Periampullary Adenomyoma: Clinicopathological Characteristics of Cases from a Single Center

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ABSTRACT

Adenomyoma is a benign tumor-like lesion, which is rarely found in the extrahepatic biliary tree, ampulla of Vater, and duodenum. Clinical findings vary by lesion location, and diagnosis often follows surgical intervention.The study included seven patients diagnosed with periampullary adenomyoma whose data were analyzed by sex, age, laboratory data, clinical and radiological features, preoperative diagnosis, surgical techniques, pathological and immunohistochemistry findings, and outcomes.

The patients were men aged 31-74 years. Abdominal pain was the most frequent clinical symptom. In most cases, the preoperative clinical impression was malignancy. Almost every case underwent Whipple resection. Submucosal nodules were the predominant macroscopic feature, and microscopically, all cases showed hyperplastic glandular lobules encircling a larger duct. In most cases, there was no atypia or mitotic figures. The most common immunohistochemical pattern was positive immunoreactivity for cytokeratin 7 (CK7), caudal-type homebox 2 (CDX2), mucin 1 (MUC1), mucin 6 (MUC6), and mucin 5AC (MUC5AC) and negative immunoreactivity for cytokeratin 20 (CK20) and mucin 2 (MUC2). Periampullary adenomyomas are manifested in different forms. Although preoperative endoscopy, endoscopic retrograde cholangiopancreatography (ERCP), frozen section, and tissue biopsy of the mass may not be definitive, they can suggest adenomyoma when used together and help avoid unnecessary pancreaticoduodenectomy, which burdens both the surgeon and the patient.

Keywords: Adenomyoma, Periampullary, Periampullary adenomyoma, Whipple's surgery

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INTRODUCTION

Adenomyoma of the hepatobiliary and gastrointestinal tract is a rare tumor-like lesion, which is assumed to be an epithelial hamartoma or a heterotopic pancreatic tissue histologically characterized by smooth muscle surrounding glandular structures with mucin-secreting epithelium (1-5). This non-malignant lesion is most frequently observed in the gallbladder or pyloric region of the stomach; however, it can rarely be found in the extrahepatic biliary tree, ampulla of Vater, and duodenum (6-10).

Clinical findings of adenomyoma vary depending on the lesion's location. Obstructive jaundice is the characteristic clinical symptom of this lesion when located in the ampulla of Vater, biliary tree, or duodenum; however, intussusception and intestinal obstruction are the most frequent findings in patients with intestinal adenomyoma. Meanwhile in patients with gallbladder adenomyoma, it is most frequently asymptomatic and is an incidental finding during surgery or autopsy (3, 11, 12).

The most effective treatment is surgical resection or endoscopic resection. Preoperative endoscopic/radiological evaluations or intraoperative frozen sections are performed to diagnose adenomyoma. However, they have all been proven insufficient to differentiate between this lesion and malignant lesions, and in some cases, pancreaticoduodenectomy is performed (1, 2, 7, 13).

This study aimed to present the clinicopathological features and the immunohistochemical findings of periampullary adenomyomas from a series of seven cases in a clinical center in Iran.

Case Reports

We retrieved seven cases of periampullary adenomyoma from the pathology files of Abualisina Hospital, affiliated with Shiraz University of Medical Sciences, during 2018-2021. The study followed the Declaration of Helsinki and received approval from the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1400.120). We extracted clinical data from surgical and pathology reports. All tissues were fixed in 10% neutral formalin and embedded in paraffin. Five-micrometer sections were cut and stained with hematoxylin and eosin (H&E). In each case, two pathologists reviewed all slides, and representative samples were selected for further immunohistochemical examination.

Immunohistochemical stains with antibodies against cytokeratin 7 (DAKO, Glostrup, Denmark; Clone OV-TL12/30; dilution, 1:50), cytokeratin 20 (DAKO; Clone Ks20.8), smooth muscle actin (DAKO; Clone 1A4; dilution, 1:40), desmin (DAKO; Clone D33; dilution, 1:20), MUC1 (SAMA TASHKHIS; Clone ZM35), MUC2 (SAMA TASHKHIS; Clone Ccp58), MUC5AC (SAMA TASHKHIS; Clone MRQ-19), and MUC6 (SAMA TASHKHIS; Clone MRQ-20) were performed using the labeled streptavidin-biotin technique. The immunohistochemistry (IHC) staining results were evaluated according to the percentage of positively stained neoplastic cells, graded as follows: negative (<5% of neoplastic cells stained), focal positive (> 5%- < 20% of neoplastic cells stained), and positive (≥20% of neoplastic cells stained).

Clinical Features and Laboratory Data:

Table 1 summarizes the clinical features. Patients' ages ranged from 31 to 74 years, with a median age of 66 years. The participants were men with no documented history of alcoholism. The most prevalent clinical manifestations were abdominal pain (n=6) and jaundice (n=3). In three cases, obstructive jaundice was present with elevated serum aminotransferases, amylase, and lipase. One patient (case 1) had a history of several hospital admissions due to acute pancreatitis 1 year before admission, and his final pathological report confirmed chronic pancreatitis. Table 2 summarizes the laboratory data.

In most cases (except case 6), the pre-operative clinical impression was malignancy, including pancreatic or ampullary carcinoma. However, all participants had an ampulla of Vater biopsy revealing no evidence of malignancy. One patient (case 1) had a fine-needle aspiration of the mass during endosonography, which revealed no malignant cells.

Except for case 6, for whom only mass resection was performed, all cases underwent Whipple resection (pancreaticoduodenectomy) due to the clinical and radiological suspicion of malignancy.

Table 1. Clinicopathological and radiological features of patients with periampullary adenomyoma

Case	Age (y/o)/ Sex	Clinical complaint	Tumor size (greatest diameter (mm)	Gross feature of lesion	Pre-operative diagnosis	Surgical Procedure	Imaging Findings	Additional findings
1	37/M	Recurrent abdominal pain	50	Single cystic	Intraductal papillary mucinous neoplasm	Whipple resection	Pancreatic mass with invasion to duodenal wall	Chronic pancreatitis

Table 1. Clinicopathological and radiological features of patients with periampullary adenomyoma

Case	Age (y/o)/ Sex	Clinical complaint	Tumor size (greatest diameter (mm)	Gross feature of lesion	Pre-operative diagnosis	Surgical Procedure	Imaging Findings	Additional findings
2	66/M	Abdominal pain and jaundice	6	Single polypoid	Pancreatic carcinoma	Whipple resection	Pancreatic head mass with CBD stone	Choledocholithiasis
3	69/M	Abdominal pain and jaundice	14	Single submucosal nodule	Periampullary carcinoma	Whipple resection	CBD dilation and mass-like lesion distal to CBD	Liver abscess
4	31/M	Jaundice and cholestasis	6	Single polypoid	Ampullary carcinoma	Whipple resection	Distal CBD stricture, CBD dilation and periampullary mass	Cholestatic hepatitis
5	74/M	Incidental finding	15	Single cystic	Periampullary carcinoma	Whipple resection	Hypoechoic mass at the medial wall of the second portion of the duodenum	Ganglioneuroma in paracaval area
6	54/M	Abdominal pain	10	Single submucosal nodule	Benign lesion	Transduodenal ampullary mass resection	CBD dilation with ampullary mass	Cholelithiasis
7	73/M	Abdominal pain	15	Single submucosal nodule	Pancreatic carcinoma	Whipple resection	Pancreatic head mass with CBD and PD dilatation	Chronic pancreatitis

CBD: common bile duct, PD: pancreatic duct

Table 2. Laboratory data of patients with periampullary adenomyoma

Case	Amylase (IU/L) (RR:<90)	Lipase (IU/L) (RR:<60)	AST (IU/L) (RR:3-40)	ALT (IU/L) (RR:3-40)	ALP (IU/L) (RR:80-306)	Total bilirubin (mg/dL) (RR:<1.3)	Direct bilirubin (mg/dL) (RR:<0.3)
1	492	12	22	28	219	0.19	0.13
2	285	131	53	74	240	4	2.6
3	500	451	115	119	377	2.1	1.1
4	290	771	76	175	405	5	3.5
5	77	14	38	20	133	0.5	0.1
6	NA	NA	14	21	151	NA	NA
7	49	23	66	42	118	0.6	0.2

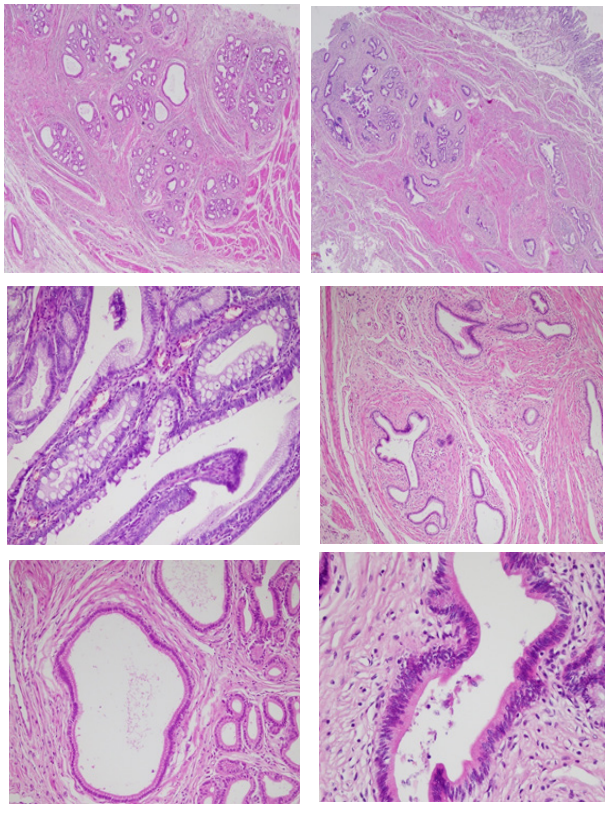
RR: Reference range, AST: aspartate aminotransferase, ALT: alanine transaminase, ALP: Alkaline phosphatase, NA: not available

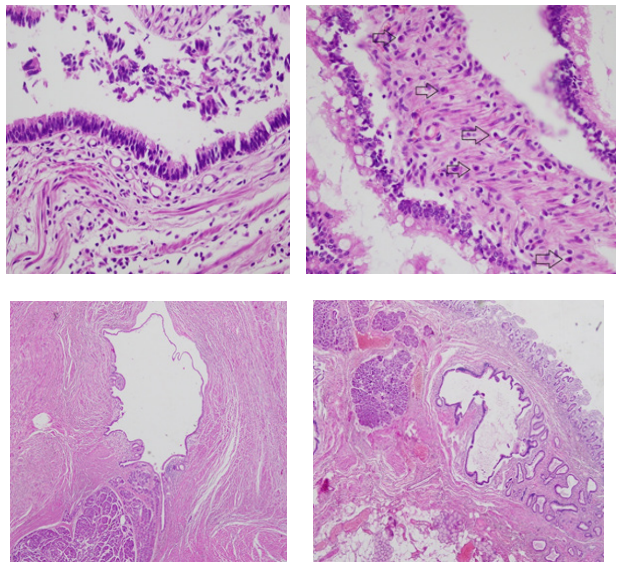
Histopathological Features:

On macroscopic examination, the lesions showed submucosal nodule formation or polypoid features ranging from 6 to 50 mm in greatest diameter. Two cases showed cystic changes grossly, and extension to the major papilla occurred in five cases and to the pancreas in three cases. The common bile ducts were dilated in all cases, measured between 0.5-1.7 cm in diameter, and the pancreatic ducts were dilated in five cases.

Microscopically, all cases had similar histopathology consisting of hyperplastic glandular lobules, mainly located in the periampullary submucosal layer. They were characterized by lobules of small glands located around a larger duct (Figures 1a and1b). The glands were lined

by a single layer of columnar mucinous epithelium. The overlying mucosa was normal in all cases, except cases No. 6 and No. 7, which showed villous formation of the mucosal layer (Figure 1c). Intestinal metaplasia with goblet cells was present in three cases (cases No. 4, 6, and 7) (Figures 1d and 1e). The cells showed no atypia and no mitotic figures in most cases (Figures 1f and 1g), and there was mild cellular atypia with elongation of nuclei and pseudostratification in some glands only in three cases (cases No.4, 6, and 7) (Figures 1h and 1i). Hyperplastic glandular lobules were surrounded by hyperplastic mesenchymal tissue consisting of muscle fibers, fibroblasts and myofibroblasts, capillaries, and varying amounts of mononuclear inflammatory cells. A significant number of mast cells were present in all cases (Figure 1j). Microscopic pancreatic heterotopia was present in the duodenal wall of five cases, continuous with the adenomyoma (Figures 1k and 1l). No adenomyomatous lesion was identified in the gallbladders and common bile ducts; however, cases No. 2 and 6 revealed choledocholithiasis and cholelithiasis, respectively. Pancreatic tissues were normal in all cases except cases No. 1 and 7, which showed chronic pancreatitis. Simultaneous liver biopsies were performed in only two cases, representing liver abscess and cholestatic hepatitis in cases No. 3 and 4, respectively.





Figures 1a and 1 b. Microscopic section shows lobules of benign small biliary glands around a larger duct surrounded by smooth muscle bundles (Hematoxylin and eosin, 40×). 1c. The overlying mucosa shows villous formation (Hematoxylin and eosin, 40×). 1d and 1e: Intestinal metaplasia with goblet cells (Hematoxylin and eosin, 100×) & (Hematoxylin and eosin, 400×). 1f and 1g: Mucinous biliary glands with columnar cells and basally located nuclei (Hematoxylin and eosin, 100×) & (Hematoxylin and eosin, 400×). 1h and 1i. Mildly atypical biliary glands with elongation of nuclei, pseudostratification, and hyperchromasia (Hematoxylin and eosin, 400×). 1j. Many mast cells (arrow) in surrounding mesenchymal tissue (Hematoxylin and eosin, 400×). 1k and 1l. Heterotopic pancreatic tissue in continuity with adenomyoma (Hematoxylin and eosin, 40×).

Immunohistochemical Features

Table 3 presents the IHC results for neoplastic epithelial and mesenchymal cells in periampullary adenomyoma cases. Glandular epithelial cells expressed membranous and cytoplasmic cytokeratin 7 (Figure 2a). Cytokeratin 20 was negative in all cases, except for focal positivity in areas with intestinal metaplasia (cases No. 4, 6, and 7) (Figure 2b). Moreover, CDX2 was positive in five cases with variable intensity (Figure 2c). MUC1 and MUC6 were positive in all cases, and MUC5AC was positive in six cases (Figures. 2d, 2e, and 2f). MUC2 was negative in all cases (Figure 2g). However, two cases showed focal reactivity in areas with intestinal metaplasia. The spindle cells around the glandular epithelial cells showed immunoreactivity for smooth muscle actin (Figure 2h).

Table 3. Immunohistochemical staining results of patients with periampullary adenomyoma

Case	Cytokeratin 7	Cytokeratin 20	CDX2	MUC1	MUC2	MUC5AC	MUC6	SMA
1	D+++	F+	F+	D+++	-	D++	D+++	+++
2	D+++	-	-	D+++	-	D++	D+++	+++
3	D+++	-	D+	D+++	-	D++	D+++	+++
4	D+++	F++	-	D+++	-	D++	F+++	+++
5	D+++	-	F+	D+++	-	-	D+++	+++
6	D+++	F++	D++	D+++	F++	D++	D+++	+++
7	D+++	F++	D++	D+++	F++	D++	D+++	+++

SMA: smooth muscle actin, D: diffuse, F: focal

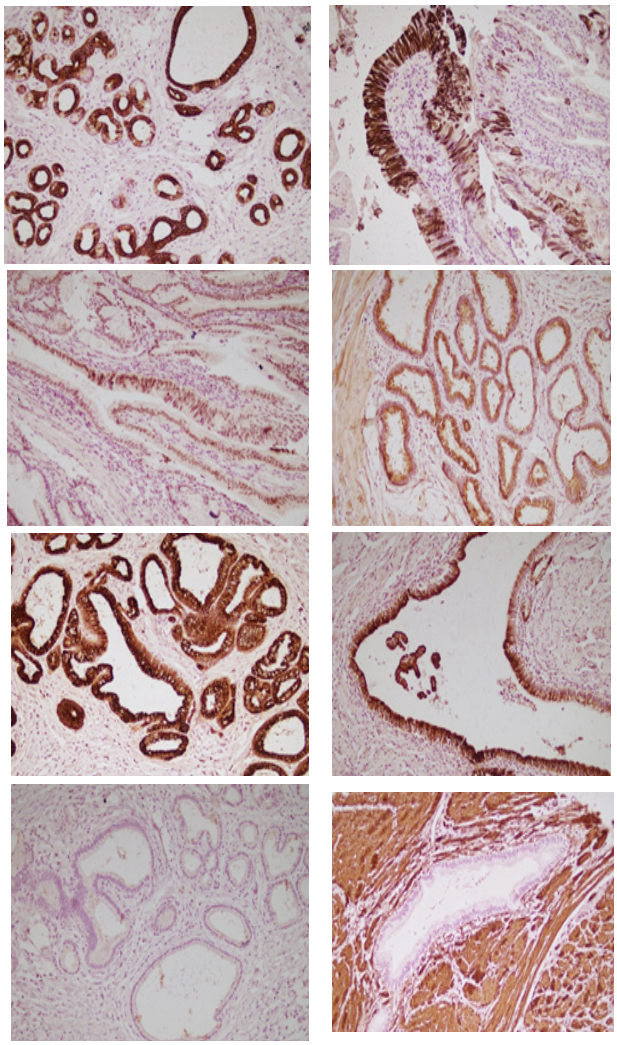


Figure 2a. Immunoreactivity for cytokeratin 7 (200×). 2b. Negative immunoreactivity for cytokeratin 20 except in areas with intestinal metaplasia (200×). 2c. Immunoreactivity for CDX2 (200×). 2d.Immunoreactivity for MUC1 (200×). 2e. Immunoreactivity for MUC6 (200×). 2f. Immunoreactivity for MUC5 AC (200×). 2g. Negative immunoreactivity for MUC2 (200×). 2h. Immunoreactivity for SMA in surrounding stroma (200×).

Follow-Up

Postoperative follow-up was performed for all patients and varied from 6 to 36 months. There was no evidence of recurrence in the patients; however, one of them died postoperatively due to a cardiovascular problem.

DISCUSSION

Adenomyoma of the hepatobiliary and gastrointestinal tract is a rare non-malignant tumor-like lesion mostly observed in the gallbladder; however, it can rarely be noticed in the ampulla of Vater, extrahepatic bile ducts, or duodenum (3, 6-9). According to the WHO classification, it has no premalignant risk (14, 15). The most effective treatment of adenomyoma is the endoscopic or surgical limited resection of the lesion, providing a favorable prognosis (5).

Adenomyoma is an incidental finding in most cases, similar to our fifth case. However, some patients with adenomyoma may present with signs and symptoms associated with the lesion's location and the patient's age. Similarly, our cases showed a variety of signs and symptoms. According to previous studies, the main clinical features are biliary obstruction (obstructive jaundice), abdominal pain, and intussusception. Gastrointestinal bleeding has also been reported as another presentation of adenomyoma (12, 16-18). Similarly, Kwon and colleagues reported a case of ampullary adenomyoma, which presented with acute recurrent pancreatitis (19).

The exact pathogenesis of adenomyoma is not completely understood; however, it has been considered a form of incomplete heterotopic pancreatic tissue (5, 16). For this reason, heterotopic pancreatic tissue may have been present in most of our cases.

On abdominal computed tomography (CT), adenomyoma of the duodenum may appear as an enhancing polypoid lesion or a submucosal tumor-like nodule on endoscopy. Endoscopic retrograde cholangiopancreatography (ERCP) can also be an effective tool for diagnosing adenomyoma; it allows inspection of the bile duct and pancreatic duct, visualization of the periampullary area, and biopsy (11). Furthermore, imaging studies show bile duct dilation in patients with biliary obstruction or stenosis caused by the lesion (12, 20). However, preoperative imaging has suggested a neoplastic or tumoral lesion in most adenomyoma cases, as in our patients. In most instances, histological identification of hyperplastic glandular lobules encircling a larger duct results in a conclusive diagnosis (16, 21-23). The value of a multi-IHC panel for differentiating ampullary lesions has only been briefly highlighted in prior papers. Although the diagnosis of periampullary adenomyoma mostly depends on histologic features on H&E slides, we used IHC to further characterize the

epithelial phenotype and compare our findings with the limited literature. Our study confirmed a pancreatobiliary immunophenotype characterized by CK7, MUC1, MUC6, and significant MUC5AC expression, while CK20 and MUC2 expression was confined to areas of intestinal metaplasia. Nevertheless, these markers have limited diagnostic utility because they overlap considerably with normal biliary epithelium and pancreatobiliary-type ampullary adenocarcinoma. As a result, IHC study should be regarded as a supplementary technique rather than a primary diagnostic method (24, 25).

Histologically, the main differential diagnosis of periampullary adenomyoma is well-differentiated adenocarcinoma of the ampulla of Vater, particularly in small biopsy or frozen-section specimens. Adenocarcinoma shows infiltrative, irregular, angulated glands; destructive stromal invasion with desmoplasia; cytologic atypia; high mitotic activity; and may demonstrate perineural or lymphovascular invasion. In contrast, adenomyoma shows a well-organized lobular arrangement of benign mucinous glands surrounding a larger duct and embedded within proliferating smooth muscle bundles without destructive invasion.

Other histological mimickers include heterotopic pancreas and reactive glandular proliferations (16, 26).

Although adenomyoma is a benign lesion, it is often misdiagnosed as carcinoma and undergoes extensive surgery.

The aforementioned tools, and even intraoperative frozen section of the mass, have been useful in differentiating a benign lesion from a malignant one; however, they are not always effective. In Menzel et al.'s study, the preoperative histopathological diagnosis of 62% of patients with a mass in the ampulla of Vater was performed using endoscopic forceps biopsies (27). Abdulkadir Bedirly and others also reported two cases of periampullary adenomyoma that underwent preoperative endoscopy, and one of the cases even had an intraoperative frozen section of the mass. Both cases underwent pancreaticoduodenectomy since adenomyoma was not diagnosed in either case (11). Furthermore, in Handra-Luca et al.'s study, six out of nine cases of adenomyoma of the papilla underwent Whipple surgery with the impression of malignancy, according to preoperative endoscopic biopsies (16). Similarly, for most of our cases, adenomyoma was not discovered until after Whipple pancreaticoduodenectomy.

Periampullary adenomyomas are manifested in different forms. Although preoperative endoscopy, ERCP, intraoperative frozen section, and tissue biopsy of the mass may not be effective, they may suggest adenomyoma when used together and prevent unnecessary pancreaticoduodenectomy that burdens both the surgeon and the patient.

DECLARATIONS:

Ethics approval and consent to participate

The study was designed in accordance with the Declaration of Helsinki, following approval from the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1400.120).

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patients' legal guardians for publication of these cases' details and any accompanying images. Copy of the written consents are available for review by the Editor-in-Chief of this journal.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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Not applicable.

AUTHORS' CONTRIBUTIONS

AMH and SN developed the study concept and design and wrote the draft manuscript. RRFS extracted the histories. NH, MHSA, and SGHR examined the patients. NH and MHSA performed the operations. AMH, VM, and SN reviewed the pathologic slides. SN and RRFS, with the input of all authors, interpreted the patient data. All authors read and approved the final manuscript.

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