Adenomyoma and Adenomyomatous Hyperplasia of the Vaterian System: Clinical, Pathological, and New Immunohistochemical Features of 13 Cases

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Adenomyoma and adenomyomatous hyperplasia of the Vaterian system are consistently benign lesions. Clinically, adenomyoma mimics frequently ampullary adenoma or carcinoma, and biopsy analysis is often difficult. The histogenesis of ampullary adenomyoma and adenomyomatous hyperplasia is still subject to debate. We present a retrospective study of clinicopathological features of 13 cases of surgically resected ampullary adenomyoma. The age of our patients was between 38 and 78 years (mean: 63 y). The preoperative diagnosis was ampullary tumor or tumor of the head of the pancreas. On macroscopy, a white, firm lesion of the ampullary wall was observed; its size ranged between 10 and 30 mm. Histologically the lesion consisted of multiple glandular structures surrounded by a fibroblastic/myofibroblastic proliferation, resulting in a "pseudo-hypertrophy" of the Vaterian system. The immunophenotype of the epithelial component was cytokeratin 7+/cytokeratin 20−, similar to that of the normal biliary and pancreatic duct system. The epithelial cells exhibited low proliferative activity. The hyperplastic myofibroblastic cells expressed smooth muscle actin. A complete pancreatic heterotopy contiguous with the adenomyoma was noted in three cases. Adenomyoma and adenomyomatous hyperplasia of the Vaterian system are benign lesions frequently treated by extensive surgery because of long-term biliary obstruction. The clinicopathological characteristics suggest either a reactive and/or a malformative, nonneoplastic nature for this lesion, which could, in some cases, develop from heterotopic pancreas. The immunophenotype of epithelial cells may be a useful tool for differentiating it from ampullary adenoma on biopsy specimens.

KEY WORDS: Adenomyoma, Adenomyomatous hyperplasia, Ampulla of Vater, Immunohistochemistry, Pancreas.

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Adenomyoma and adenomyomatous hyperplasia are rare benign lesions of the hepatobiliary and gastrointestinal tract, with most cases described in the gallbladder. A few cases have been reported elsewhere in the gastrointestinal tract, including the stomach, small bowel, bile ducts, and ampullary region (1). Adenomyoma and adenomyomatous hyperplasia of the Vaterian system are consistently benign lesions. In the WHO classification, adenomyoma is defined as a tumorlike lesion of extrahepatic bile ducts (2). Morphological analyses of individual cases have been reported previously (3–17). The total number of cases does not exceed 20. The neoplastic or malformative origin of this lesion is still subject to controversy. Despite its benign nature, adenomyoma is responsible for biliary obstruction and is misdiagnosed with carcinoma or adenoma. Therefore it is treated frequently by extensive surgery.

The aim of this study was to present the clinicopathological features of adenomyoma and adenomyomatous hyperplasia of the Vaterian system from a series of 13 cases treated by extensive surgery. We report new immunohistochemical features of adenomyoma and discuss their potential interest in the interpretation of biopsy specimens of ampulla of Vater.

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PATIENTS AND METHODS

The cases were selected from the records of the Department of Pathology, Beaujon Hospital, Clichy and Saint Antoine Hospital, Paris, France. Thirteen cases of adenomyoma and adenomyomatous hyperplasia of the Vaterian system were identified according to the WHO diagnostic criteria (2) on pancreaticoduodenectomy specimens obtained between 1988 and 2001. Clinical data were obtained from the surgical and pathology reports.

All specimens were fixed in 10% formalin and embedded in paraffin, and 4-μm sections were stained using hematoxylin and eosin stain. In each case, all slides were reviewed by four observers (AHL, BT, AC, JFF). Representative samples were selected for immunohistochemical techniques.

Immunohistochemical stains with antibodies against cytokeratin 7 (DAKO, Glostrup, Denmark; Clone OV-TL12/30; dilution, 1:50), cytokeratin 20 (DAKO; Clone Ks20.8; dilution, 1:50), smooth muscle actin (DAKO; Clone 1A4; dilution, 1:40), desmin (DAKO; Clone D33; dilution, 1:20), and Ki67 antigen (Immunotech, Marseille, France; Clone Mib-1; dilution, 1:50) were performed according to the labeled streptavidin-biotin technique. Before applying antibodies, an antigen retrieval was conducted in an autoclave (121° C, 10 min), using a citrate phosphate buffer (0.01 mol/L, pH 6.0).

Five cases of ampullary adenoma with low-grade dysplasia (3 biopsies and 2 surgical specimens) were tested for antigens to Ki67 and cytokeratins 7 and 20.

RESULTS

Clinical Features

See Table 1 for a summary. The patients' age ranged from 38 to 78 years (mean: 63 y). The male-female sex ratio was 6:7. Nine cases came from one hospital, and these cases represented 3.5 of all pancreaticoduodenectomies performed during the same period of time. The patients were hospitalized for jaundice (5 cases), epigastric abdominal pain (3 cases), pain in the right upper quadrant (2 cases), and non-icteric cholestasis with cholangitis (1 case). In three cases, there were several episodes of abdominal pain with increased levels of serum aminotransferases and increased serum alkaline phosphatase in two cases. In three cases, the lesion was discovered during systematic examination for other complaints (renal tumor, diarrhea). No patient had a documented history of alcoholism. The interval between surgical resection and first symptoms was determined in 10 cases; it varied from 1 to 60 months (mean: 10 mo). In 9 cases, this interval was between 1 and 8 months, whereas only 1 case (Case 10) reached the maximum of 60 months.

Diagnostic Procedures and Treatment

Radiological procedures included CT scans, echographies, endoscopies, and endosonographies. On endoscopy, the major papilla showed a nodular pattern without ulceration. Endosonography showed intraampullary heterogenous lesions (measuring between 10 and 21 mm) stenosing the terminal part of the common bile duct. The proximal common bile duct and/or the pancreatic duct were dilated in all and respectively four cases, with bicanalar dilation in four cases (31%).

Sphincterotomy was performed in seven cases, but symptoms reappeared.

Biopsies of the ampullary region were made in nine cases. Inflammatory and regenerative changes were present in three cases. Atypical glandular structures were seen in six cases, and a diagnosis of

TABLE 1. Clinical Features of 13 Cases of Adenomyoma and Adenomyomatous Hyperplasia of the Vaterian System

	Age/Sex	Clinical Complaints	Imaging Features	Preoperative Histologic Diagnostic
Case 1	64/M	Abdominal pain	Heterogenous intra-ampullary lesion, 11 mm	Not made (brush cytology: atypical cells)
Case 2	61/M	Jaundice, epigastric pain	No lesion	Adenoma
Case 3	73/M	Incidental (kidney tumor)	Heterogenous intra-ampullary lesion, 21 mm; lithiasis of the CBD	Inflammatory changes
Case 4	67/F	Jaundice	Intra-ampullary lesion, 15 mm	Adenocarcinoma
Case 5	54/F	Incidental (diarrhea)	Intra-ampullary lesion, 20 mm	Adenoma
Case 6	55/M	Cholestasis	Hypoechogenic intra-ampullary lesion 15 mm in the vaterian system	Severe dysplasia
Case 7	71/F	Pain in the right upper quadrant	Hyperechogenic intra-ampullary lesion, 10 mm	Muscle fibers, glandular structures
Case 8	78/F	Jaundice, cholestasis	Tumour of the head of the pancreas	Not made
Case 9	49/F	Pain in the right upper quadrant	NA	Hyperplastic glandular structures, inflammatory changes
Case 10	38/F	Abdominal pain	NA	Low grade dysplasia
Case 11	67/M	Jaundice	Thickening of the terminal CBD wall	Not made
Case 12	74/M	Jaundice	Heterogenous intra-ampullary lesion, 20 mm	Not made
Case 13	72/F	Incidental (traumatism)	Intra-ampullary lesion, 10 mm	Adenocarcinoma

M = male; F = female; NA = not available; CBD = common bile duct.

dysplastic adenoma of the ampulla of Vater was suggested (in 3 of these cases, a sphincterotomy procedure was performed before biopsy; Fig. 1). Brush cytology was performed in one case and suggested epithelial atypia. In three cases, no histological or cytological sampling was made, and surgical treatment was decided upon because of the severity of clinical complaints. The preoperative diagnosis was of ampullary tumor (12 cases) and tumor of the head of the pancreas (1 case).

Pancreaticoduodenectomy was performed in all cases.

Pathology Findings

On macroscopic examination in all the cases the lesions were similar: the ampulla of Vater and the terminal portion of the common bile duct exhibited a firm, grossly nodular lesion measuring 10 to 30 mm in diameter. The lesion extended to the major papilla in seven cases (Fig. 2). The overlying mucosa was normal, without ulceration. The common bile duct was dilated in all cases, whereas choledocholithiasis was detected in only two cases. The pancreatic duct was dilated in four cases and measured between 0.9 and 1.5 cm in diameter. In three cases there were associated pancreatic abnormalities: annular pancreas in one case (Case 3) and pancreas divisum in two cases (Cases 7 and 11).

On histologic examination, in all cases the lesion had the same morphology. It consisted of hyperplastic glandular lobules mainly located in the ampulla of Vater with coexisting lesions in the major papilla. These were characterized by lobules of small glands located around a larger duct (Fig. 3). These glands were covered by a single-layer epithelium, consisting of cuboidal and columnar cells. The cells showed no atypia and no mitotic figures (Fig. 4). In all cases, some glands showed cystic changes. The hyperplastic glandular lobules were surrounded by hyperplastic mesenchymal tissue,

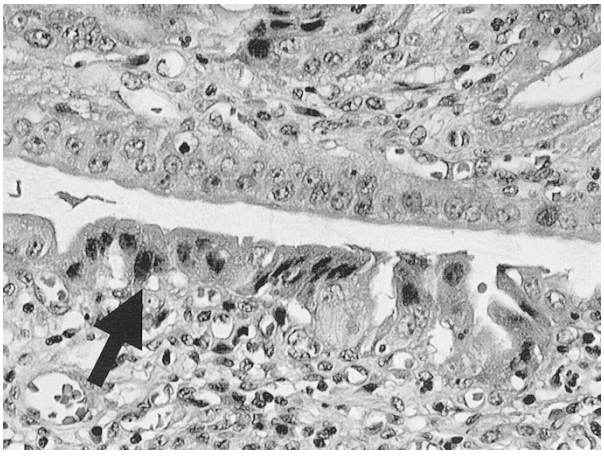

FIGURE 1. Reactive changes in the epithelial component of adenomyoma: pseudostratification, irregular, hyperchromatic nuclei (***arrow***). Note the adjacent, mild inflammatory infiltrate in the fibroblastic/myofibroblastic component.

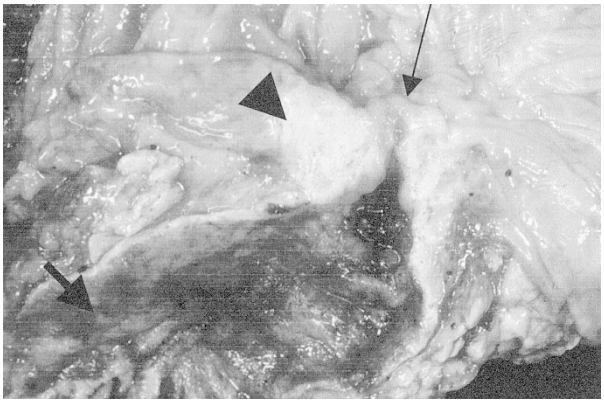

FIGURE 2. Macroscopic features of adenomyoma: a white, firm thickening of the ampullary region (***arrowhead***). Stenosis of the terminal common bile duct (***small arrow***) and dilatation of its proximal part (duodenal wall: ***long arrow***).

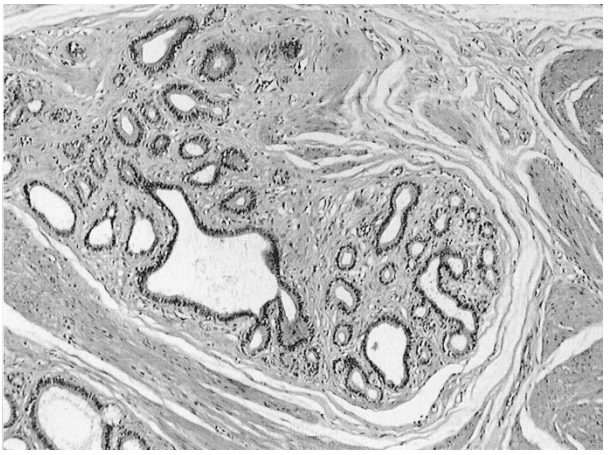

FIGURE 3. Microscopic features of adenomyoma: glandular structures (some cystically dilated) surrounded by a fibroblastic/myofibroblastic cell proliferation. Hematoxylin and eosin stain.

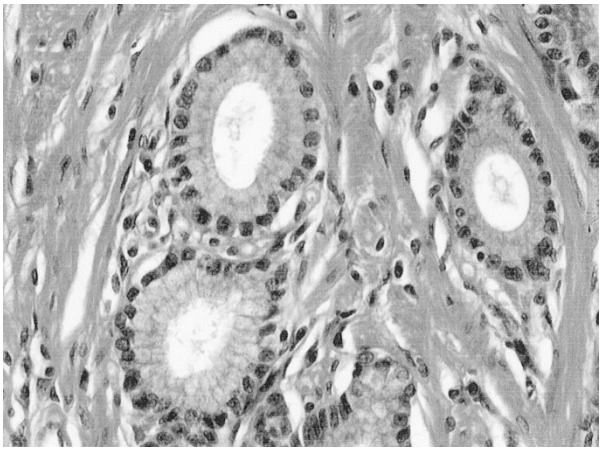

FIGURE 4. At high magnification the glandular structures are lined by an unistratified epithelium. The cells are columnar, without nuclear atypia.

which consisted of muscle fibers, fibroblasts and myofibroblasts, capillaries, and varying amounts of mononuclear inflammatory cells. The nonspecific inflammatory changes were probably secondary to sphincterotomy or caused by the inflammatory process accompanying migration of gallstones.

Pancreatic heterotopia with both exocrine and endocrine pancreatic tissue was present in the duodenal wall (seen on microscopy, but not macroscopically) in three cases, in continuity with the adenomyoma. In two of these cases, the adenomyomatous lesions were present both in the ampullary region and in the pancreatic tissue (beyond the duodenal wall). In all these cases, transition zones showing progressive loss of acinar structures and endocrine islets and the increase of ductular-glandular structures were noted (Fig. 5).

Adenomyomatous lesions, similar to those observed in the Vaterian system, were present in the gallbladder in two cases (Cases 1 and 2) of the nine cases in which gallbladder specimens were available. In one case (Case 11), pancreas heterotopia was present in the antrum. Cholelithiasis was present in three cases and common bile duct lithiasis, in two cases.

Pancreatic tissue was normal except for in one case (Case 4), in which a benign pancreatic mucinous cystic tumor (measuring 0.5 cm) was discovered on microscopic examination.

Liver biopsies were performed during the surgical procedure in six cases. Portal tract lesions caused by bile duct obstruction were observed in two cases, whereas in the other four cases there were no hepatic lesions.

Immunohistochemical Features

Proliferative activity was estimated by immunohistochemical staining with Ki67 antibody. Rare cells with a positive nuclear staining were present in the epithelial component of the lesion, but no nuclear staining was observed in the myofibroblastic component. The number of positive stained nuclei in the epithelial component of adenomyoma (2%) was similar to normal epithelia of the pancreatic duct system and less than in adenoma, where it was between 10 and 40%.

Glandular epithelial cells, similarly to the cases of the normal epithelial cells of the pancreatic and biliary duct system, expressed cytokeratin 7 (Fig. 6) and did not express cytokeratin 20, which in turn was strongly expressed in the duodenal mucosa and in all adenomas of low-grade dysplasia. Three of five adenomas expressed cytokeratin 7.

The myofibroblastic phenotype of most spindle cells was confirmed by a strong cytoplasmic expression of smooth muscle actin (Fig. 7) without desmin expression. Rare spindle cells co-expressed desmin. Some of the spindle cells were smooth muscle actin and desmin negative.

Follow-Up

Postoperative follow-up was available in 10 patients and varied between 1 and 73 months. There was no evidence of recurrence in any of the patients.

DISCUSSION

Adenomyoma is a rare lesion that has been observed in different sites throughout the gastrointestinal tract, most frequently in the gallbladder. According to the WHO classification (2), adenomyoma and adenomyomatous hyperplasia are defined as ductlike structures accompanied by hyperplasia of smooth muscle cells. Single cases of adenomyoma have been reported in the stomach, small bowel,

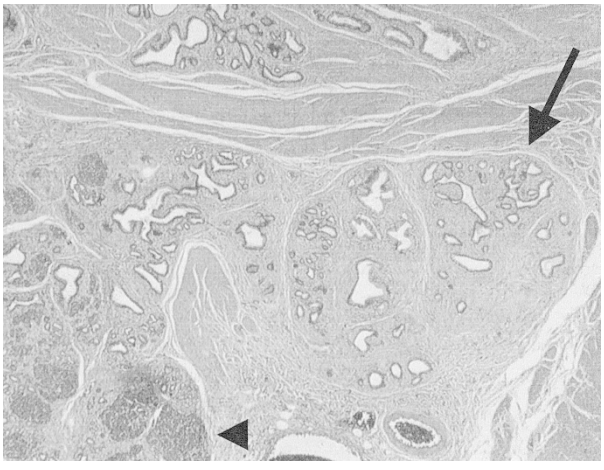

FIGURE 5. Microscopic features of adenomyoma: multiple lobular lesions (***arrow***) with "transition zones" between characteristic adenomyomatous lesions and pancreatic lobules (***arrowhead***). Hematoxylin and eosin stain.

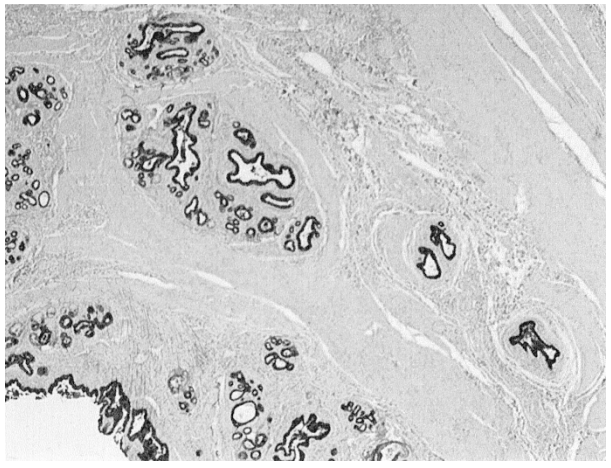

FIGURE 6. Immunohistochemical features of adenomyoma: strong cytokeratin 7 expression in the epithelial lining of glandular structures.

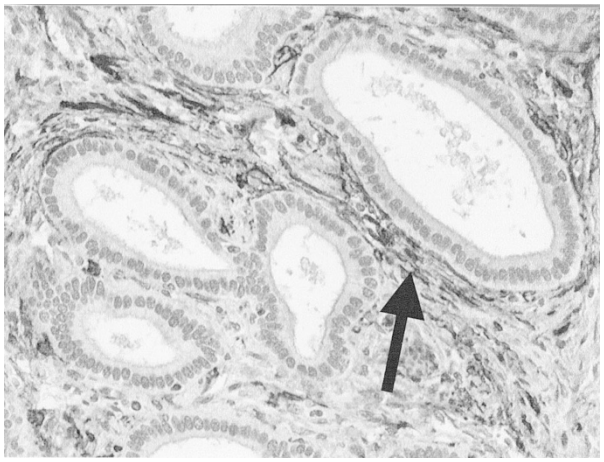

FIGURE 7. Immunohistochemical features of adenomyoma: smooth muscle actin expression in the myofibroblastic component (***arrow***).

and extrahepatic bile ducts. The diagnosis of adenomyoma of the Vaterian system, unlike its counterparts in the rest of the digestive tract, has important clinical consequences. Although it is a benign lesion, it is often treated with extensive surgery, and histological examination is required for precise diagnosis.

Real incidence of adenomyoma and adenomyomatous hyperplasia of the Vaterian system is difficult to appreciate as different names (*adenomyoma, adenomyomatosis, myoepithelial hamartoma, adenomyomatous hyperplasia*) are used to designate the same histological lesion. The incidence is high if we consider published series of unselected postmortem examinations: small lesions (2–5 mm) of adenomyoma of the Vaterian system were reported in 50 to 70% of the cases (18–20), 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.

In the present series, adenomyoma was diagnosed only in adult patients (mean age: 63 y, range: 38–78 y). Clinical complaints initially suggested long-term biliary tract obstruction and relapsed after sphincterotomy. In three cases, several episodes of increase of serum aminotransferase level were noted. Elevated serum alkaline phosphatase are observed in rare cases, and this may favor the clinical confusion with carcinoma. In 23% of cases, the lesion was discovered incidentally in patients presenting unrelated conditions.

Preoperative imaging procedures suggested a diagnosis of Vaterian system tumor. The lesion was of small size, and its benign or malignant nature was not established before surgery.

Endoscopic biopsies of the papilla (performed in 9 cases) showed epithelial cell atypias that were considered to be highly suggestive for dysplasia in 66.6% of the cases. This was interpreted retrospectively as secondary to a regenerative postsphincterotomy process and/or to the reactive changes related to migration of gallstones. The immunophenotype of epithelial cells that was observed in our cases, which includes a low proliferative activity, the expression of cytokeratin 7, and no cytokeratin 20 expression, could serve as criteria in differentiating adenomyoma and adenomyomatous hyperplasia from a neoplastic process (*e.g.*, adenoma, carcinoma) on ampullary biopsy specimens, especially when reactive atypia caused by inflammation are superimposed. This proposal has to be tested prospectively.

There is no established treatment for Vaterian system adenomyoma and adenomyomatous hyperplasia. Endoscopic sphincterotomy should be required to restore adequate biliary drainage (6). When a surgical treatment is decided, intraoperative frozen section could be of help, leading to a limited resection instead of extensive surgery such as pancreaticoduodenectomy (8, 21). Hammarström *et al.* (6) suggest a careful follow-up in such cases, with repeated endoscopic retrograde cholangiographies to ensure the benign diagnosis. In our series, pancreaticoduodenectomy was performed in all cases because of either severe and/or recurrent symptoms after sphincterotomy. In our series, ampullectomy could have been the treatment in eight cases.

The diagnosis of adenomyoma and adenomyomatous hyperplasia was made on histologic examination of surgically resected specimens. The histological aspect of adenomyoma is characterized by multiple lobules of glands, mainly located in the muscle layers of the Vaterian system, resulting in a hypertrophy of the sphincter of Oddi (which also explains the stenosis of the terminal common bile duct). Involvement of the major papilla can be present. The lobular formations consist of small glands disposed around a larger gland and surrounded by a myofibroblastic and fibroblastic proliferation. This mesenchymal component is rather composed of fibroblasts and myofibroblasts (with smooth muscle actin expression and without desmin expression), but it may contain sparse smooth muscle cells. This component may contain also sparse capillaries and inflammatory cells.

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 (22). The presence of hyperplastic smooth muscle tissue can be explained by secondary muscle proliferation caused by some stimulus emanating from misplaced epithelium, or by muscle misarrangement, or by an aberrant growth invading and distorting normal muscle (23). The possibility of a complex form of heterotopia, of

enteropancreatic type, could explain the presence within the same lesion of different glandular epithelial patterns such as Brunner's glands and intestinal glands (24). However, pancreatic heterotopic tissue was present in only three of our cases.

Martin *et al.* (25) 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, that leads to poorly defined lobules (26). Fernandez-Cruz and Pera (27) considered adenomyoma as part of an involutive process of fibroadenomatous type due to increasing age. Other authors, such as Narita and Tokoyama (11), point out the possibly inflammatory nature of this lesion.

Independently from its histogenesis, adenomyoma is considered as benign and slow growing, but its potential neoplastic nature cannot be excluded (16). A recent review identified a total of 30 cases of malignant change arising in heterotopic pancreas. In seven cases, the heterotopic pancreas was of Type III (adenomyoma), and in one case carcinoma arose in an ampullary location (28). Another possible method of evolution is the formation of cysts with inflammatory changes, leading to duodenal wall cystic dystrophy as has already been described by our group (29).

In conclusion, Vaterian system adenomyoma is a rare lesion of clinical importance. In the majority of cases, although it is an entirely benign lesion, this is because of its clinical and endosonographic similarities to ampullary tumors like adenoma, or carcinoma. The clinicopathological features of ampullary adenomyoma are consistent with a heterotopic nature, but other mechanisms (hyperplasia of intramural glands of the common bile duct, reactive changes caused by the inflammatory response to migration of gallstones) are probably involved in the genesis of this lesion.

Immunohistochemical criteria like cytokeratin 7 expression and a low proliferative activity (Ki67) in the epithelial cells and no cytokeratin 20 expression should be considered in the analysis of ampullary biopsy specimens to differentiate adenomyoma and adenomyomatous hyperplasia from adenomatous or carcinomatous ampullary tumors, and thus considered as well in the decision to perform a limited surgical resection.

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