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# 팽대부 선근종의 임상적, 병리학적, 면역조직화학염색의 특징

최용혁, 김미진, 한정호, 윤순만, 채희복, 윤세진, 강민호[1], 성노현[2], 최재운[3], 박선미
충북대학교 의과대학 내과학교실, 영상의학교실[1], 병리학교실[2], 외과학교실[3]

## Clinical, Pathological, and Immunohistochemical Features of Adenomyoma in the Ampulla of Vater

Yong Hyeok Choi, Mi Jin Kim, Joung-Ho Han, Soon Man Yoon, Hee Bok Chae, Sei Jin Youn, Min Ho Kang[1], Rohyun Sung[2], Jae Woon Choi[3] and Seon Mee Park

Departments of Internal Medicine, Radiology[1], Pathology[2], and Surgery[3], Chungbuk National University College of Medicine, Cheongju, Korea

**Background/Aims:** Ampullary adenomyoma is a benign lesion whose malignant potential has yet to be confirmed. Despite its benign nature, adenomyoma is frequently misdiagnosed as a carcinoma or adenoma and is overtreated by extensive surgery. This study was performed to analyze the clinical, pathological, and immunohistochemical features of adenomyomas in the ampulla of Vater.
**Methods:** Nine cases of adenomyoma in the ampulla of Vater, diagnosed in Chungbuk National University Hospital between 2008 and 2011, were enrolled in this study. We reviewed the clinical data on the symptoms, laboratory data, and radiologic findings of the abdominal computed tomography and endoscopic retrograde cholangiopancreatography. For pathological analysis, all the slides were reviewed by one pathologist, and immunohistochemical stainings with antibodies against cytokeratin 7 (CK7), cytokeratin 20 (CK20), α-smooth muscle actin (α-SMA), and Ki-67 antigen were performed.
**Results:** All the cases were CK7 positive and CK20 negative. A strong cytoplasmic expression of α-SMA was confirmed in all cases. The Ki-67 index was less than 1% in eight cases and 5% in one case. Four cases underwent endoscopic papillectomy, and one case received surgical ampullectomy during colorectal cancer surgery. Five cases that underwent endoscopic or surgical treatment remained symptom-free for three years. Four cases that were closely observed with repeated endoscopic examinations exhibited no interval changes in the papillary lesions.
**Conclusions:** Endoscopic biopsy and immunohistochemistry can aid in the diagnosis of ampullary adenomyomas. Endoscopic papillectomy or surgical ampullectomy is adequate for the treatment of symptomatic ampullary adenomyomas. **(Korean J Gastroenterol 2013;62:352-358)**

**Key Words:** Adenomyoma; Ampulla of Vater; Immunohistochemistry

## INTRODUCTION

Adenomyoma in the Vaterian system is a benign tumor-like lesion that has been observed in different sites throughout the biliary tract. The gallbladder is the most frequent location of this lesion, which is rarely found in the extrahepatic biliary tract or ampulla of Vater.[1] Unlike adenoma, adenomyoma is a benign lesion whose malignant potential has not yet been confirmed. According to the World Health Organization (WHO) classification, adenomyoma is defined as a pro-

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**교신저자:** 박선미, 361-711, 청주시 흥덕구 내수동로 52, 충북대학교 의과대학 내과학교실
**Correspondence to:** Seon Mee Park, Department of Internal Medicine, Chungbuk National University College of Medicine, 52 Naesudong-ro, Heungdeok-gu, Cheongju 361-711, Korea. Tel: +82-43-269-6019, Fax: +82-43-27-3252, E-mail: smpark@chungbuk.ac.kr

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liferation of duct-like structures accompanied by hyperplasia of smooth muscle cells.[2] The symptoms of adenomyoma vary depending on the location. Adenomyoma of the gallbladder is asymptomatic or results in mild upper quadrant abdominal pain. However, adenomyoma of the biliary tree can produce symptoms such as jaundice or abdominal pain due to the obstruction of bile flow.[3,4] Despite its benign nature, adenomyoma is responsible for biliary obstruction and is usually misdiagnosed as a carcinoma or adenoma. As a result, the lesion is frequently overtreated with radical surgery.[1] Proper diagnosis before surgery can prevent unnecessary radical resection and result in treatment with endoscopic papillectomy or close observation.

This study was performed to analyze the clinical, pathological, and immunohistochemical features of adenomyomas in the ampulla of Vater and to compare the clinicopathologic features of other cases reported in the literature.

## SUBJECTS AND METHODS

Nine cases of adenomyoma in the ampulla of Vater, diagnosed in Chungbuk National University Hospital (Cheongju, Korea) between 2008 and 2011, were enrolled in this study. They were identified according to the WHO diagnostic criteria of endoscopic biopsy or resected specimens by pathologic review. Four patients underwent endoscopic papillectomy, while surgical ampullectomy was performed on one patient during colorectal cancer surgery. Four patients were diagnosed by repeated endoscopic examinations with biopsy and were followed-up for more than two years. Clinical data about any symptoms such as abdominal pain or jaundice and laboratory tests of AST, ALT, GGT, ALP, and total bilirubin at the time of diagnosis were obtained from the medical records. The findings from the abdominal CT and ERCP were reviewed by one radiologist. The size of the ampullary lesion, the diameter of the common bile duct (CBD), and the presence of intrahepatic duct (IHD) dilatation were evaluated. Endoscopic findings including the size of the mass and gross features were reviewed by one endoscopy expert. For the pathological data, all the specimens were fixed in 10% formalin and embedded in paraffin. The 4-μm sections were stained using a hematoxylin and eosin stain. In each case, all the slides were

**Table 1.** Clinical Features of Nine Cases of Ampullary Adenomyoma

| Case | Age (yr)/sex | Clinical symptom | CT finding | Endoscopic finding | Endoscopic biopsy | AST/ALT (IU/L) | ALP (IU/L) | T-bil (mg/dL) | Treatment |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 70/M | Abdominal pain | Focal enhancing lesion at AOV and CBD dilation (14 mm) | 15 mm sized ampullary mass with granularity | Adenomyoma | 78/30 | 268 | 0.57 | Endoscopic papillectomy |
| 2 | 71/M | Abdominal pain | Non-specific finding | 12 mm sized ampullary mass | Adenomyoma | 55/92 | 432 | 1.83 | Endoscopic papillectomy |
| 3 | 72/M | Incidental | 15×12 mm sized well defined nodule at AOV and CBD dilatation (13 mm) | 12 mm sized ampullary mass with villous mucosa | Dysplasia →adenomyoma | 25/11 | 180 | 0.36 | Endoscopic papillectomy |
| 4 | 53/M | Abdominal pain | Non-specific finding | 10 mm sized lobulated lesion | Chronic inflammation →adenomyoma | 25/33 | 300 | 1.46 | Endoscopic papillectomy |
| 5 | 75/M | Incidental (colon cancer) | Focal enhancing lesion at AOV with diffuse IHD and CBD dilatation (11 mm) | Bulging and lobulated papilla | Adenomyoma | 17/15 | 230 | 0.55 | Surgical ampullectomy |
| 6 | 75/F | Incidental | Mass (11 mm) at AOV, IHD and CBD dilatation (10 mm) | Bulging and lobulated papilla | Adenomyoma | 23/16 | 251 | 0.36 | Close observation |
| 7 | 64/F | Incidental | CBD dilatation (10 mm) | Bulging papilla | Adenomyoma | 44/33 | 178 | 0.60 | Close observation |
| 8 | 57/F | Incidental | Non-specific finding | Enlarged and lobulated papilla | Atypical epithelial proliferation →adenomyoma | 36/29 | 174 | 1.02 | Close observation |
| 9 | 65/F | Incidental | Not performed | Bulging and lobulated papilla | Adenomyoma | 29/28 | 273 | 0.56 | Close observation |

M, male; F, female; AOV, ampulla of Vater; CBD, common bile duct; IHD, intrahepatic duct; T-bil, total bilirubin.

reviewed by one pathologist. Representative sections were selected for immunohistochemical staining with antibodies against cytokeratin 7 (CK7; Clone OV-TL12/30; dilution, 1 : 400; Neomarker, Fremont, CA, USA), cytokeratin 20 (CK20; Clone Ks20.8; dilution, 1 : 100; Novocastra, Newcastle Upon Tyne, UK), α-smooth muscle actin (α-SMA; asm-1; dilution, 1 : 150; Novocastra), and Ki-67 antigen (MM1; dilution, 1 : 150; Novocastra). CK7, CK20, and α-SMA findings were expressed as positive or negative, while Ki-67 antigen findings were expressed as a percentage of the immunohistochemistry.

## RESULTS

### 1. Clinical features

The ages of the nine patients ranged from 57 to 75 years (mean, 66.9 years), and the male to female ratio was 5 : 4. Six patients were asymptomatic, and lesions were found incidentally during esophagogastroduodenoscopy for health screening in five patients and during a colon cancer work-up in one patient. Three patients complained of mild nonspecific abdominal pain. Six patients had normal laboratory tests, and three patients exhibited mild abnormalities in liver function tests (Table 1).

### 2. Radiologic and endoscopic features

An abdominal CT scan showed mild dilatation of the CBD (10-14 mm) in five cases, mild dilatation of the IHD in two cases, and the presence of a focal nodular mass (11-15 mm) in four cases (Fig. 1). Three cases showed no abnormal findings on the abdominal CT scan. Endoscopic findings of an enlarged major papilla and villous granularities around the papillary orifice could be identified in all cases (Fig. 2). All the cases were diagnosed by endoscopic examinations including gross findings and biopsies. One case underwent extensive biopsy after sphincterotomy. Six cases were diagnosed in the first examination, while three cases were diagnosed in the second examination.

### 3. Pathologic features

Upon histologic examination, all the cases had similar morphology. Hyperplastic glandular lobules were located in the ampulla of Vater and were covered by a single-layer epithelium consisting of cuboidal and columnar epithelial cells. There was no cellular atypia or mitotic changes in these cells. The hyperplastic glandular lobules were surrounded by hyperplastic mesenchymal tissues that consisted of muscle fibers, fibroblasts, myofibroblasts, and capillaries (Fig. 3A). The proliferative activity estimated by the Ki-67 index was determined to be less than 1% in eight cases and 5% in one case (Fig. 4B). The myofibroblastic phenotype of most spindle cells was confirmed by the strong cytoplasmic expression of α-SMA without desmin expression in all cases (Fig. 4C, D). All the cases were CK7 positive and CK20 negative (Fig. 4E-H). This means that that the glandular epithelial cells of the adenomyoma originated from pancreatic or biliary tracts.

### 4. Treatments

Four patients underwent endoscopic papillectomy as the usual procedure. After grasping the mass at the base with a

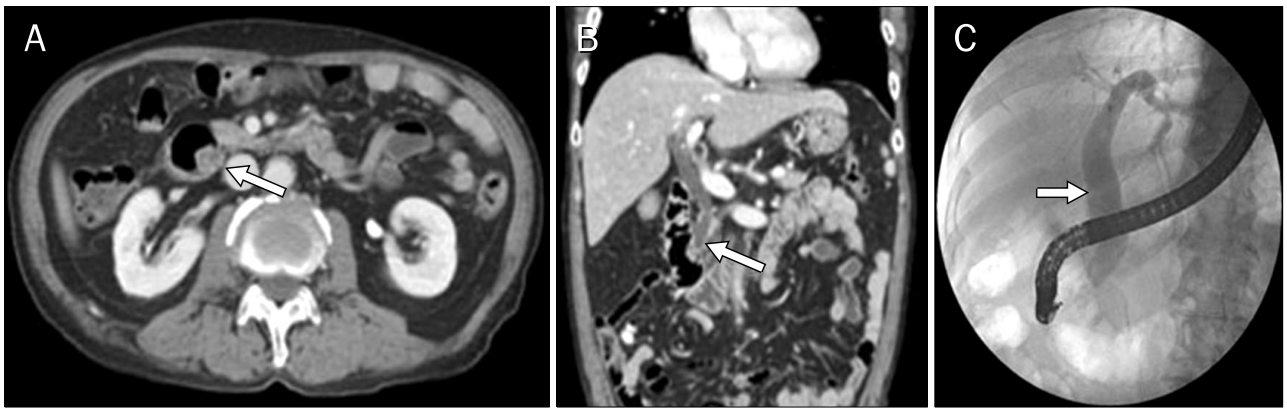


**Fig. 1.** Radiologic findings of adenomyomas in the ampulla of Vater. Abdominal CT (A, axial view; B, coronal view) showed a 1.4-cm mass protruding into the duodenal lumen with a dilated common bile duct (arrows). (C) Endoscopic retrograde cholangiopancreatography showed a dilated biliary tract (arrow).

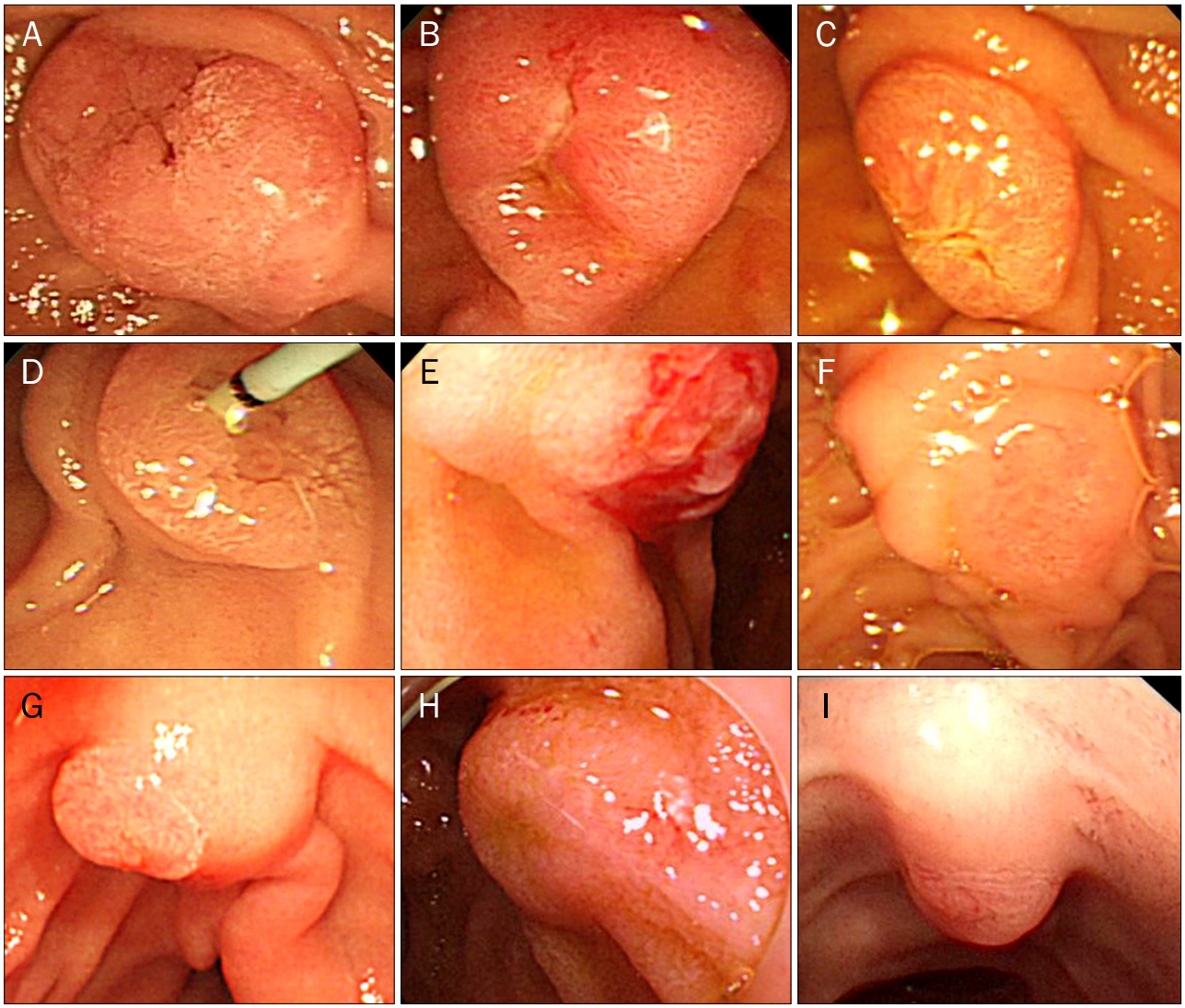


**Fig. 2.** Endoscopic view of ampullary adenomyomas. Enlarged major papilla and villous and granular mucosa around the papillary orifice could be identified in all cases; each case matched from A to I.

snare, resection was performed using electrocautery (Fig. 3). A pancreatic stent was placed before or after the papillectomy by the decision of an endoscopist. Surgical ampullectomy was completed on one patient during colorectal cancer surgery. During the procedure, no remarkable complications occurred. Five cases that underwent endoscopic or surgical resection remained symptom-free for three years. The four cases that received repeated endoscopic examinations exhibited no interval changes in the papillary lesions.

## DISCUSSION

The histological aspect of ampullary adenomyoma is characterized by multiple lobules of glands, mainly located in the muscle layers of the Vaterian system, resulting in hypertrophy of the sphincter of Oddi.[1] The histogenesis of adenomyomas remains uncertain. The most widely accepted hypothesis is that these lesions may represent a form of an incomplete heterotopic pancreas.[1] Some authors explained the histogenesis of adenomyomas as hyperplastic smooth muscle tissue undergoing secondary muscle proliferation because of the stimulation of misplaced epithelium, muscle mis-arrangement, or by an aberrant growth invading and distorting the normal muscle tissue.[5] Other authors considered adenomyoma as a part of an involutive process of the fibroadenomatous type due to aging.[6]

Adenomyoma of the ampulla of Vater is very rare. Four cases of adenomyoma in the ampulla of Vater have been re-

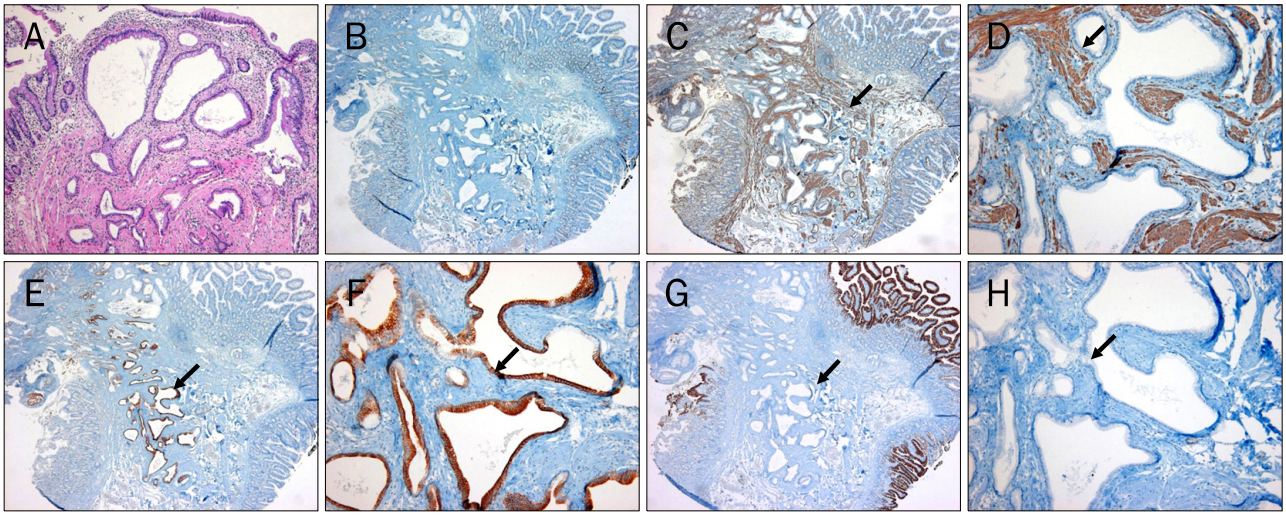


**Fig. 3.** Pathological and immunohistochemical features of adenomyomas in the ampulla of Vater. (A) Hyperplastic glandular lobules covered by a single layer of epithelium were surrounded by hyperplastic mesenchymal tissues composed of muscle fibers, fibroblasts, myofibroblasts, and capillaries (H&E, ×200). (B) Immunohistochemical staining with the Ki67 antibody level detected at less than 1% (×40). (C, D) α-SMA expression (arrows) in the myofibroblastic component (×40 and ×400, respectively). (E, F) Strong CK7 expression (arrows) in the epithelial lining of the glandular structures (×40 and ×400, respectively). (G, H) No CK20 expression (arrows) in the epithelial lining of the glandular structures (×40 and ×400, respectively).

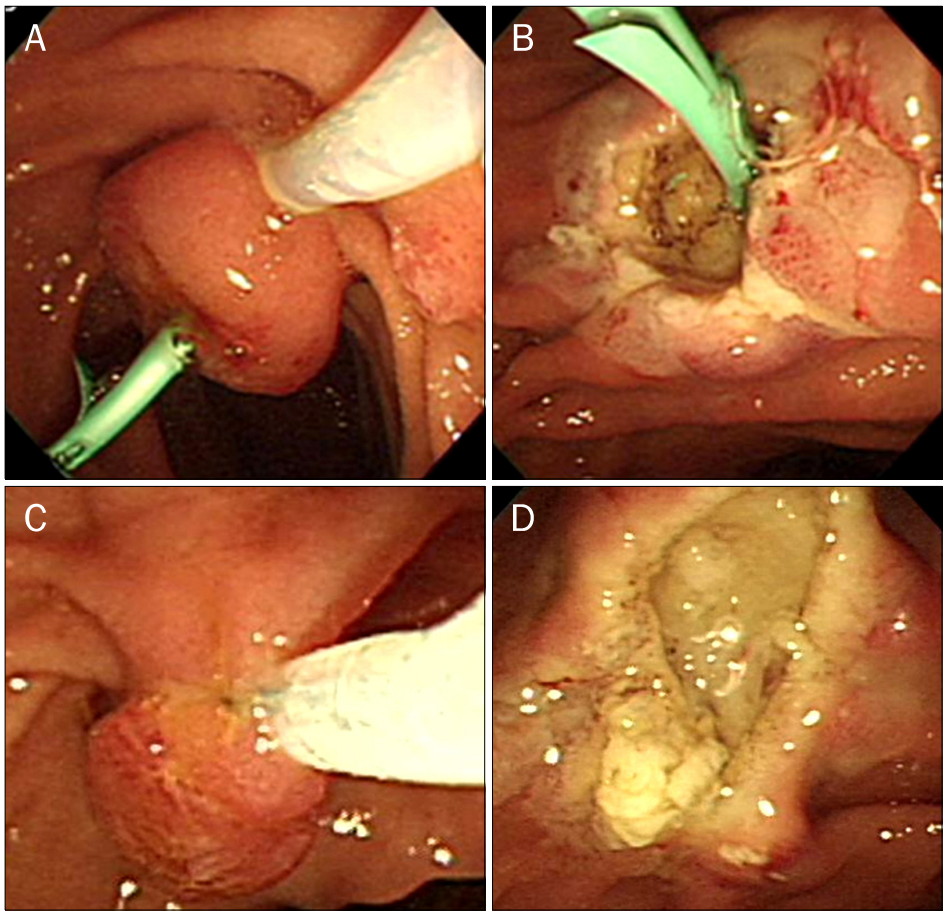


**Fig. 4.** Endoscopic papillectomy for an ampullary adenomyoma. (A) Endoscopic papillectomy was performed after pancreatic stent insertion. (B) Endoscopic view of the stent placed in the biliary duct after papillectomy. (C) Endoscopic papillectomy was performed without prior pancreatic stent insertion. (D) Endoscopic view of the major papilla after papillectomy.

**Table 2.** Clinical Features of Four Cases of Ampullary Adenomyoma Reported in the Literature

| Year published | Age (yr)/ sex | Clinical symptom | CT finding | Endoscopic finding | Endoscopic biopsy | AST/ALT (IU/L) | ALP (IU/L) | T-bil (mg/dL) | Treatment |
|---|---|---|---|---|---|---|---|---|---|
| 2004[7] | 69/M | Hyperbilirubinemia | Mass at CBD with diffuse BD and PD dilatation | Normal AOV | Chronic inflammation | 33/13 | 62 | 1.8 | Pancreaticoduodenectomy |
| 2005[8] | 56/M | Mild jaundice | Mass at AOV with BD dilatation | Sessile mass | Focal nuclear atypia | Normal | 350 | 2.1 | Surgical ampullectomy |
| 2007[9] | 74/F | Abdominal pain (pancreatitis) | Diffuse dilated CBD without focal mass | Even and firm nodular mass with a granular and villous mucosa (after EST) | Muscle proliferation without atypia | 31/11 | 85 | 1.3 | Piecemeal resection with an electrocautery snare |
| 2010[10] | 69/M | Abdominal pain/ anorexia | Diffuse BD and PD dilatation | Bulging and lobulated papilla | Focal adenoma | 57/20 | 85 | 0.9 | Endoscopic papillectomy |

M, male; F, female; CBD, common bile duct; BD, bile duct; PD, pancreatic duct; AOV, ampulla of Vater; EST, endoscopic sphincterotomy; T-bil, total bilirubin.

ported in Korea (Table 2).[7-10] Most cases presented with abdominal pain, jaundice, pancreatitis, or dilatation of the bile duct that was found through an abdominal CT scan. Endoscopic treatment was performed in two cases,[9,10] while surgical resection was performed in two other cases.[7,8] One case, which presented with acute pancreatitis, was treated by large particle biopsy using an electrocautery snare. After treatment, the patient's symptoms improved, and no complications occurred during the follow-up period.[9] The other case underwent papillectomy by ERCP.[10] Two cases[7,8] underwent surgical resection by pancreaticoduodenectomy because malignant potential could not be excluded (Table 2).

Since ampullary adenomyoma is a benign lesion, extensive surgery is not necessary. Most patients who have received extensive surgery such as pancreaticoduodenectomy have had their ampullary adenomyomas mistaken as malignant lesions before surgery. Proper preoperative diagnosis can prevent unnecessary surgery. The proper diagnosis of ampullary adenomyomas is sometimes very difficult to achieve through abdominal CT or endoscopic exam. Usually the diagnostic accuracy of endoscopic biopsies for ampullary lesions is not high. One study showed that it was 62%.[11] However, our study revealed that all cases could be diagnosed as adenomyomas through a single or repeated endoscopic biopsies. Most cases showed an enlarged nodular papilla with villous and mucosal granularities. ERCP can be a useful diagnostic tool for this lesion since it allows for the inspection of the periampullary region and visualization of the pancreatobiliary tracts. Moreover, a proper biopsy specimen can be taken from the lesion through a lateral scope rather than a direct scope.[12] Pathologic features of specimens obtained from proper biopsy sites are useful for diagnosis when there are findings of glandular epithelial cells and smooth muscles proliferation without mitosis or atypical changes.

There is no established treatment for adenomyoma of the ampulla of Vater. Endoscopic sphincterotomy or endoscopic papillectomy can be helpful in restoring adequate biliary drainage.[3] When surgical treatment is decided upon, intraoperative frozen sections could result in limited resection instead of extensive surgery.[13,14] In this study, we performed endoscopic treatment or close observation in all cases except one. One patient underwent surgical ampullectomy during colorectal cancer surgery, since malignancy could not be completely excluded despite the preoperative diagnosis of benign disease.

Special immunohistochemical staining can show the characteristics of adenomyoma compared to neoplastic lesions in the ampulla of Vater. One study reported on the function of mucin in differentiating between adenomyoma and malignant lesions.[15] Another study investigated the expression patterns of CK7, CK20, $\alpha$-SMA, and Ki-67 in ampullary

adenomyomas.[16] CK7 and CK20 are expressed differently according to the tissue origin - CK7 is expressed from the pancreato-biliary tract, while CK20 is expressed from the gastrointestinal tract. These markers have been used for the identification of the site of origin. α-SMA recognizes the alpha-smooth muscle isoform of actin and exhibits no cross reaction with actin from fibroblasts, striated muscle, or myocardium. α-SMA stains smooth muscle cells in vessel walls, gut walls, and the myometrium.[17] The Ki-67 protein is a cellular marker for proliferation and is present during all active phases of the cell cycle, but is absent from resting cells.[18] A low expression level of Ki-67 means that the adenomyoma has no malignant potential. Our nine cases showed compatible patterns of adenomyoma that consisted of CK7 positive epithelium, α-SMA positive smooth muscle hyperplasia, and a low Ki-67 index.[1,8] These results indicate that immunohistochemistry performed on the biopsy tissue of the ampulla of Vater before treatment is very useful in confirming ampullary adenomyoma.

In conclusion, awareness of ampullary adenomyomas is very important in clinical situations because of their clinical and endoscopic similarities to ampullary tumors like adenomas and carcinomas. The method of treatment based on the diagnosis can affect the patient's quality of life. The immunohistochemical results of ampullary lesions can help in the diagnosis of adenomyoma. Immunohistochemical criteria like CK7 positivity and CK20 negativity and low proliferative activity in the epithelial cells should be considered as indicating a diagnosis of adenomyoma of the ampulla of Vater. Endoscopic biopsy and immunohistochemistry of ampulla of Vater lesions can help in the diagnosis of ampullary adenomyoma. Endoscopic papillectomy or surgical ampullectomy is sufficient for symptomatic ampullary adenomyomas. For asymptomatic ampullary adenomyomas, close observation is recommended. These strategies can avoid unnecessary surgeries such as laparotomies or pancreaticoduodenectomy.

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